Imaging Neurodegeneration in MS

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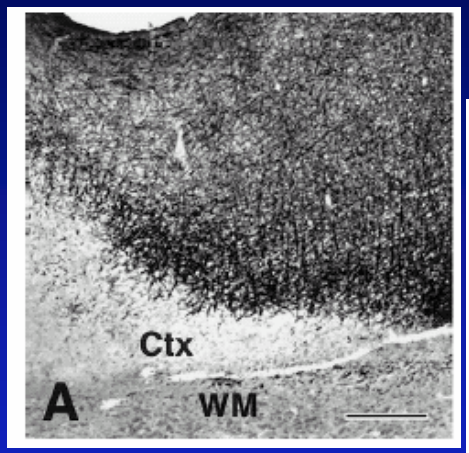
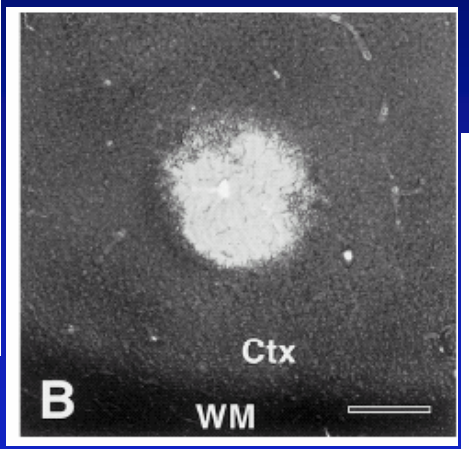
Axonal changes in MS

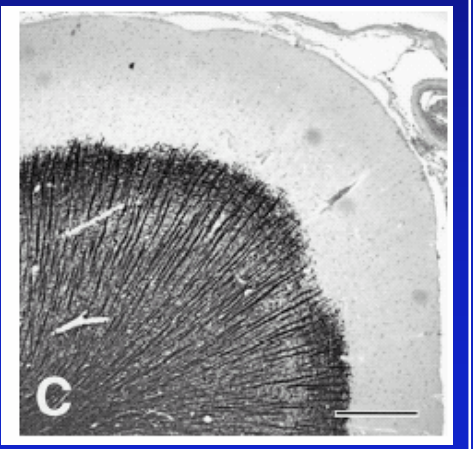
Pathological study of normal appearing regions

Axonal Degeneration in MS Spinal cord

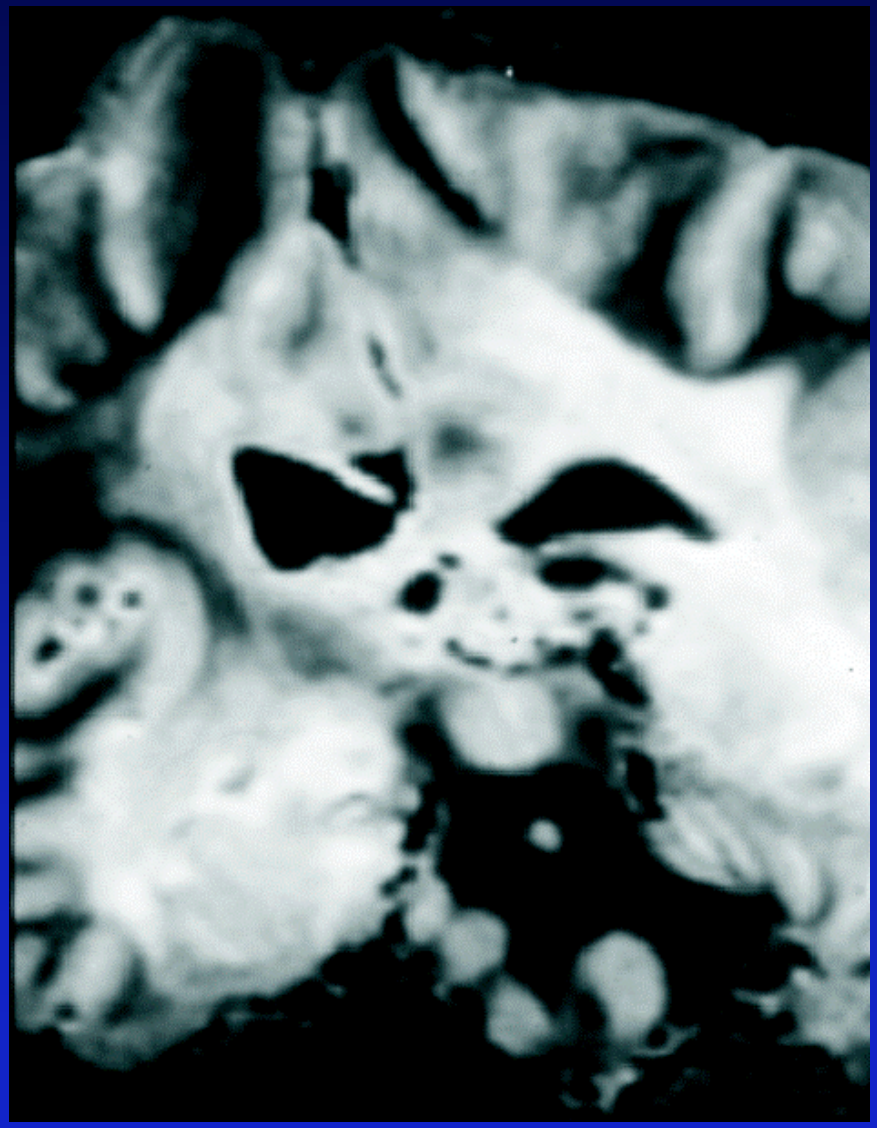
Cortical Lesions in MS Brains

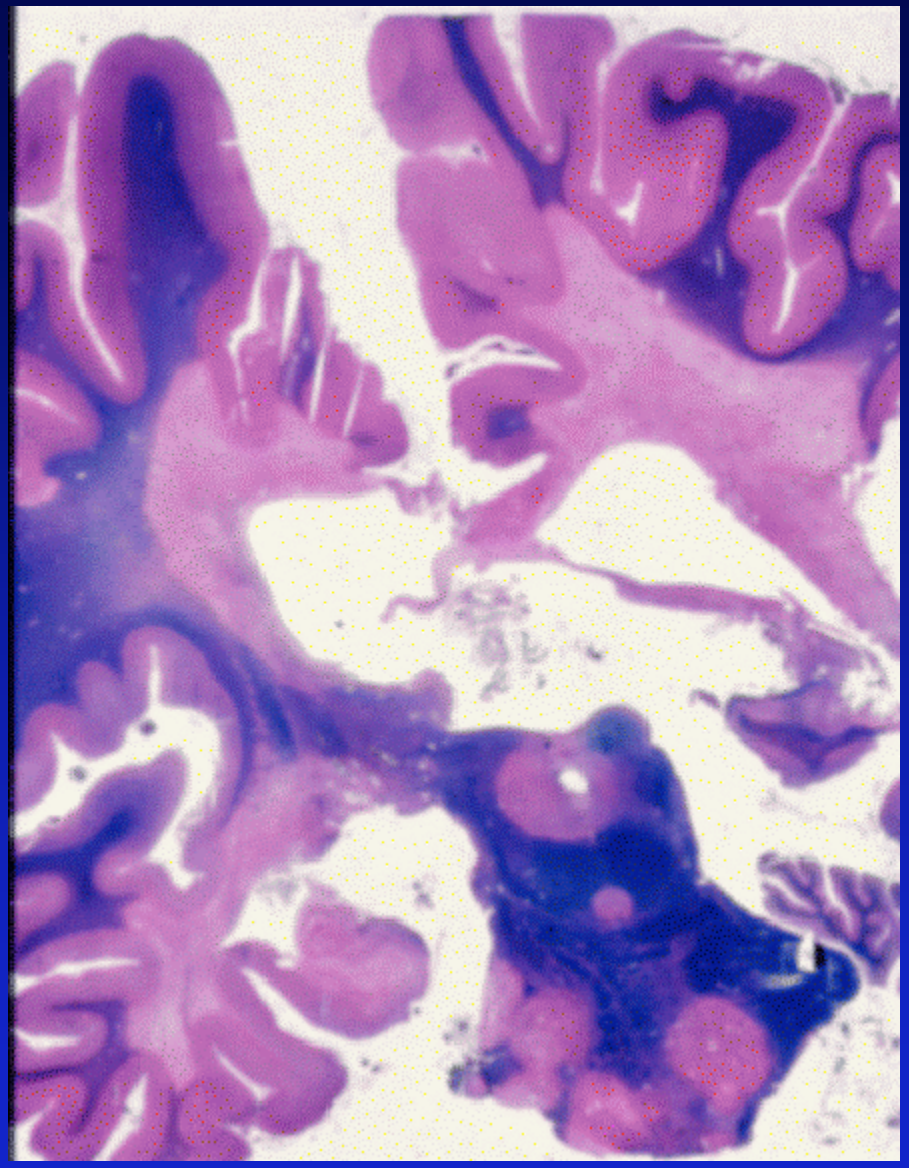






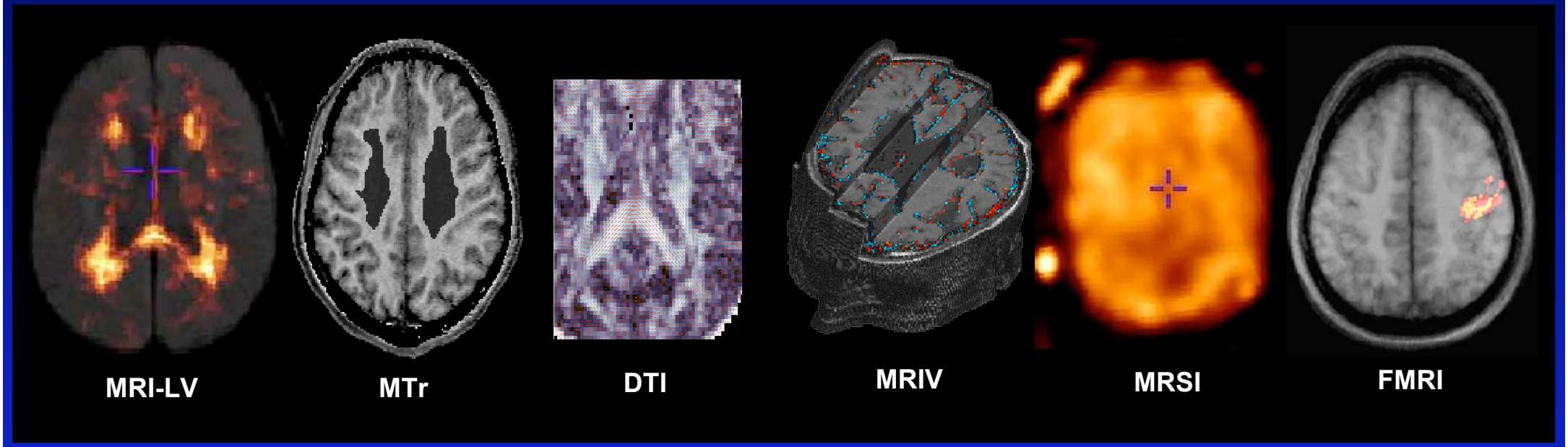
Peterson JW et al Ann Neurol 2001





Kindly provided by Don Paty, MD

Quantitative MR



Multiple Sclerosis

MR measures of Neuro-Axonal Damage

- *T1-weighted WM lesions (Black Holes)*
- *MT ratio*
- *N-Acetylaspartate*
- *Brain Atrophy*

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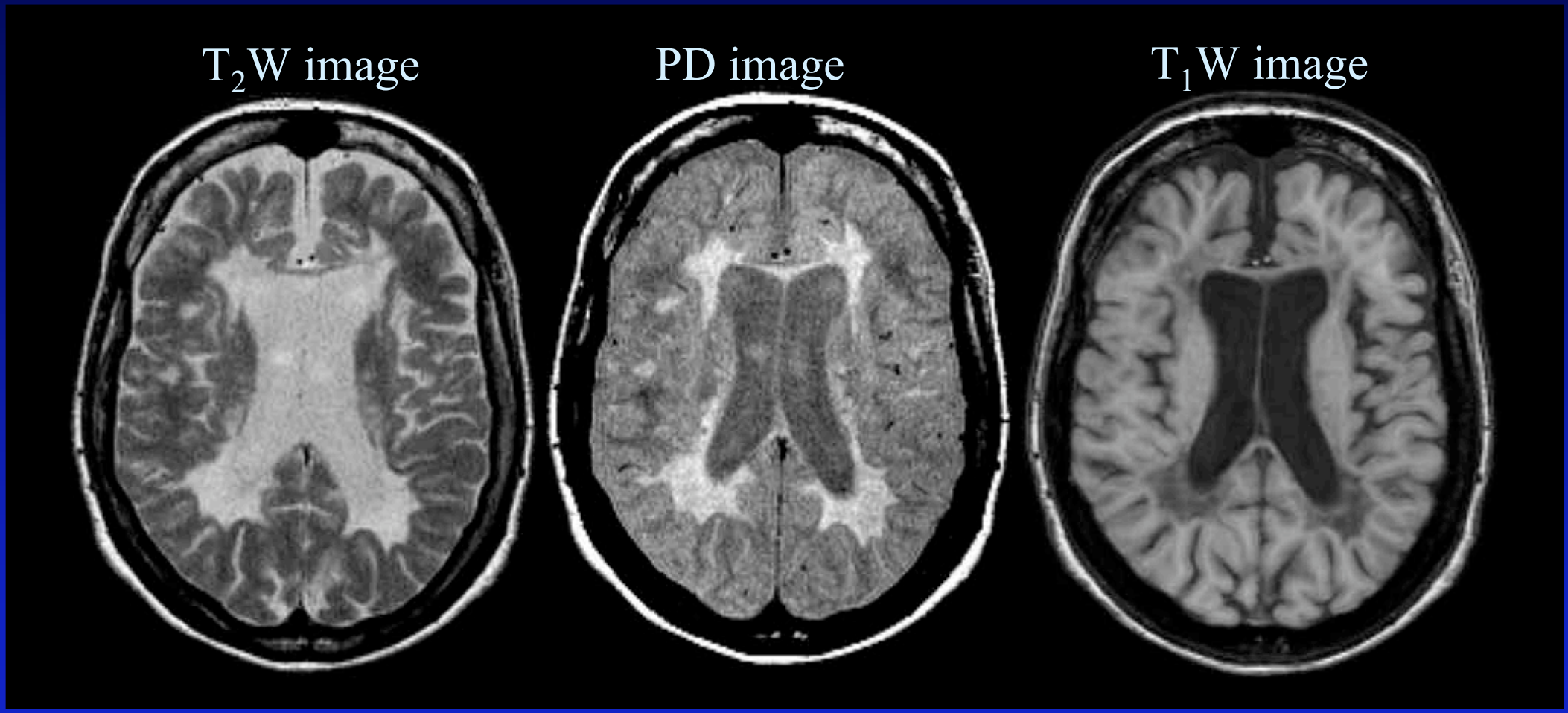
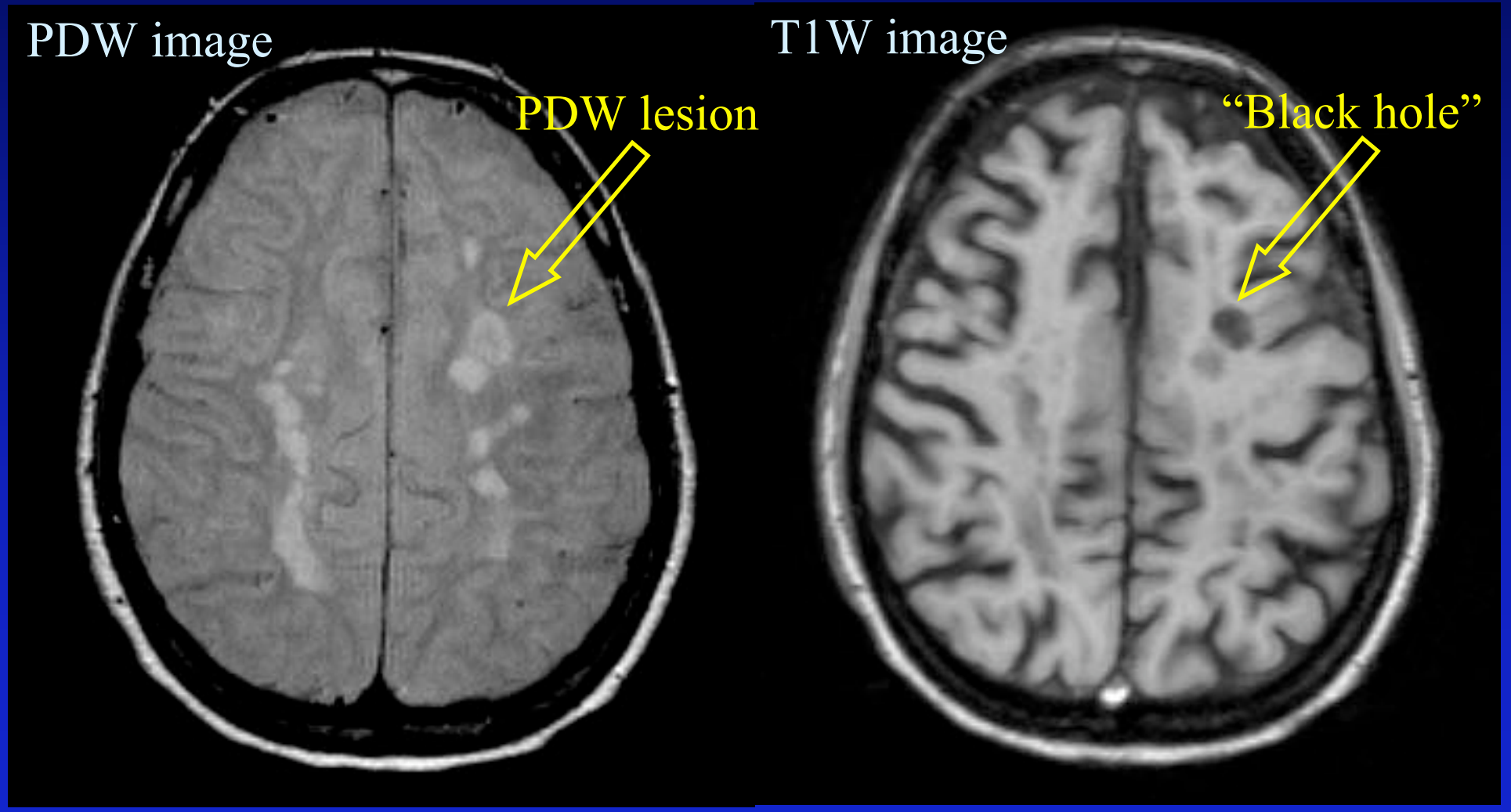
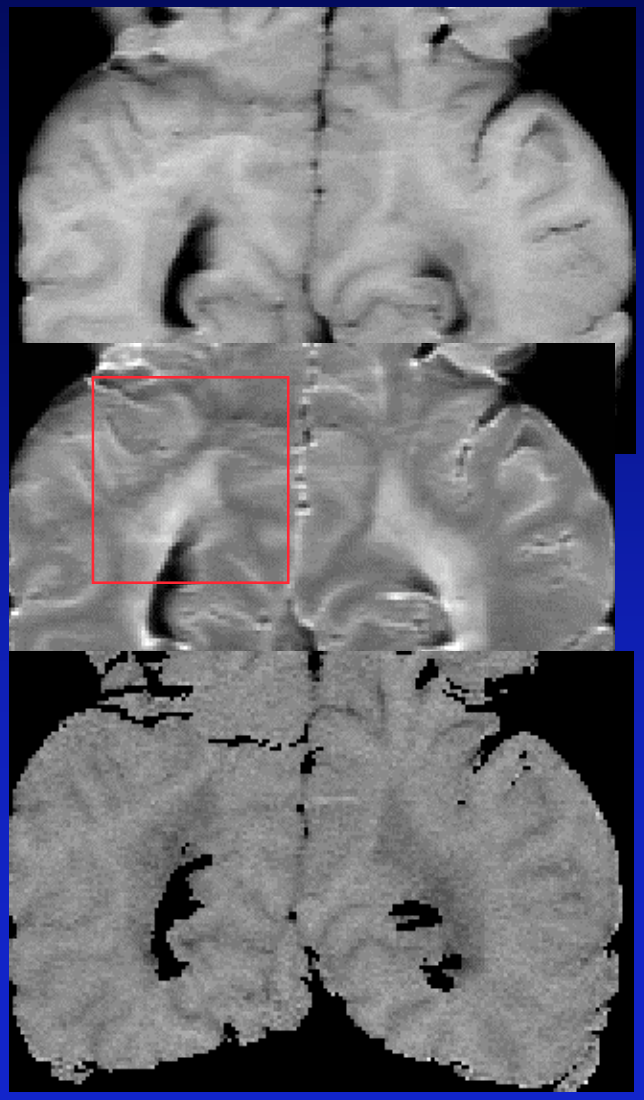
Conventional MRI in MS

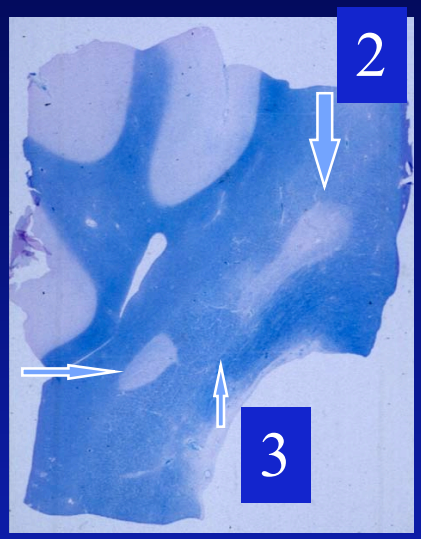


Cerebral MS Lesions



Imaging Irreversible Tissue Damage



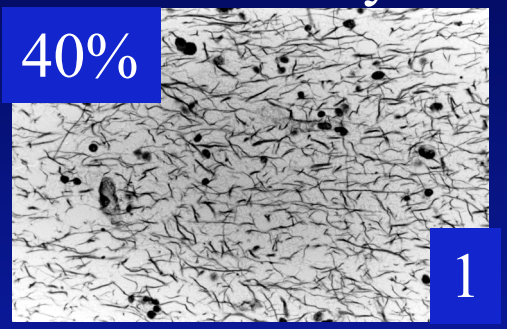


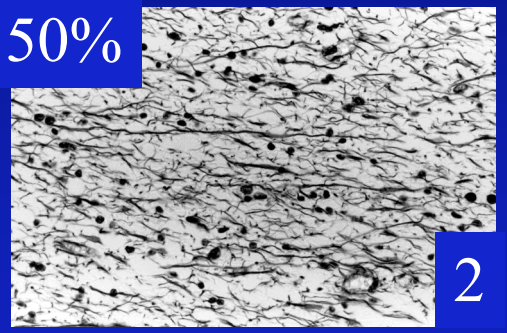
1: strongly hypointense,

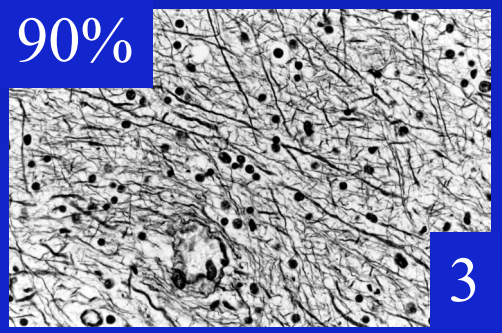
2: mildly hypointense,

3: slightly hypointense

Axonal density





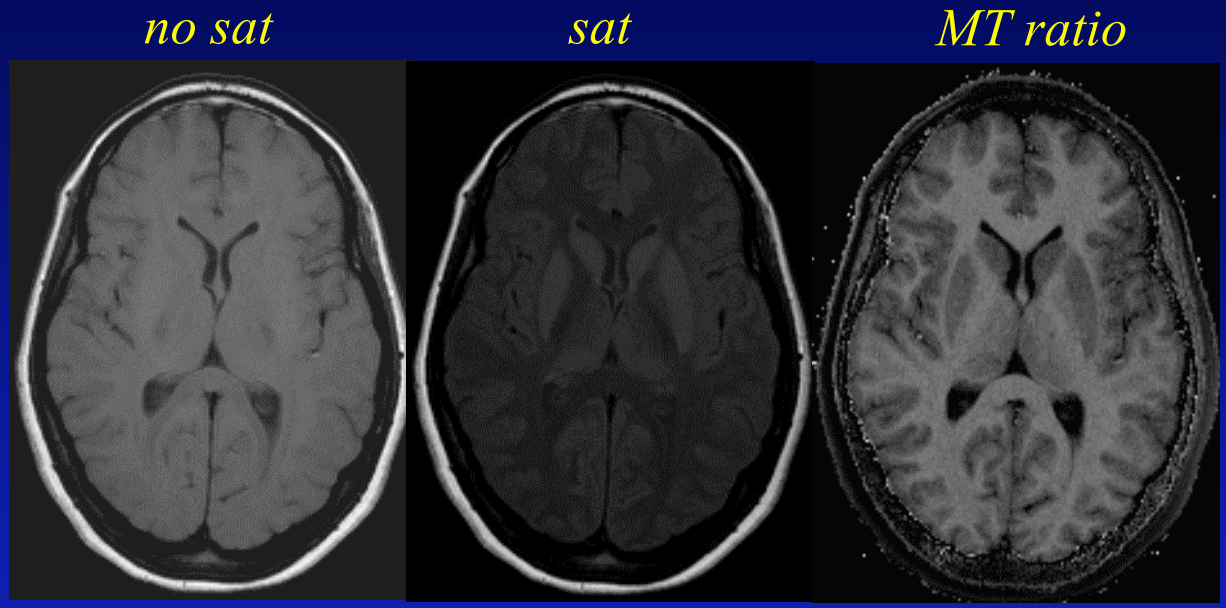


Multiple Sclerosis

MR measures of Neuro-Axonal Damage

- *T1-weighted WM lesions (Black Holes)*
- *MT ratio*
- *N-Acetylaspartate*
- *Brain Atrophy*

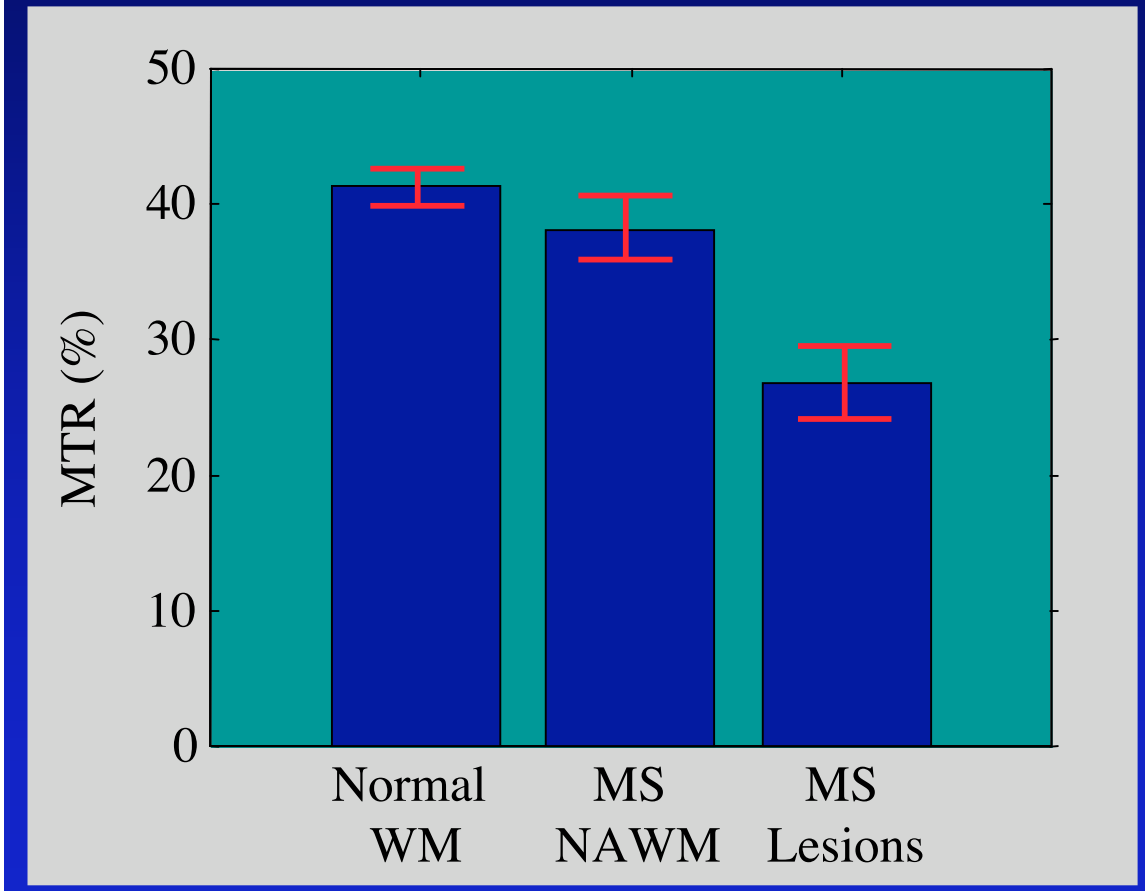
Magnetization Transfer (MT)



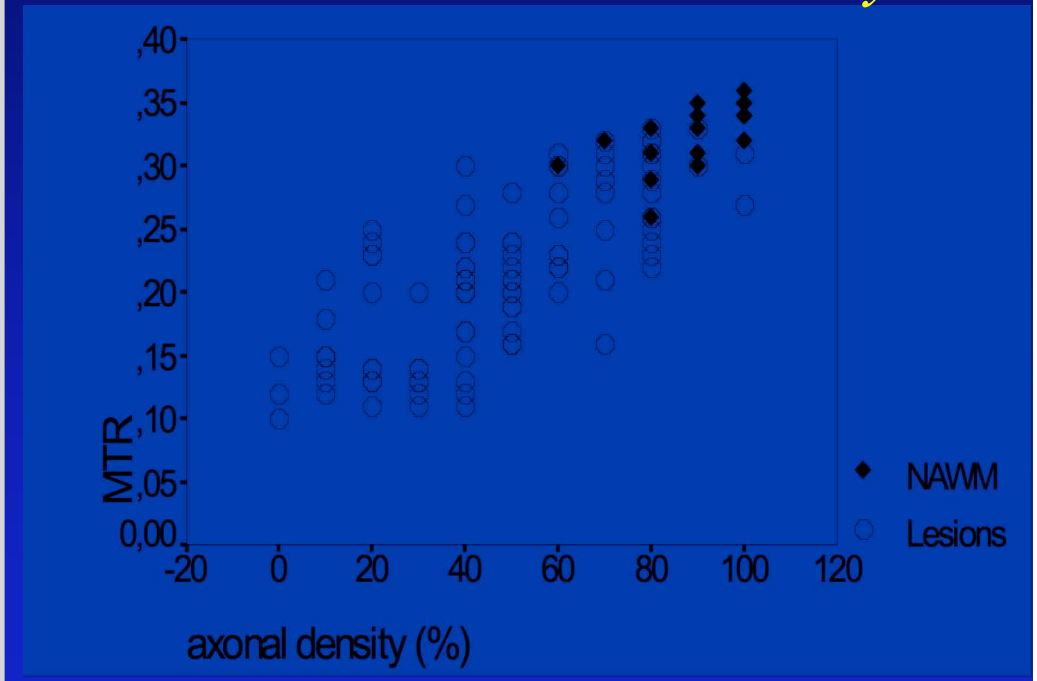
- *MT imaging of the brain is based on the interactions between the free water protons and protons attached to macromolecules*
- *Low MTr indicates a reduced capacity of the protons in the brain tissue matrix to exchange magnetization with the surrounding water protons*

Imaging Tissue Damage

MTr in WM

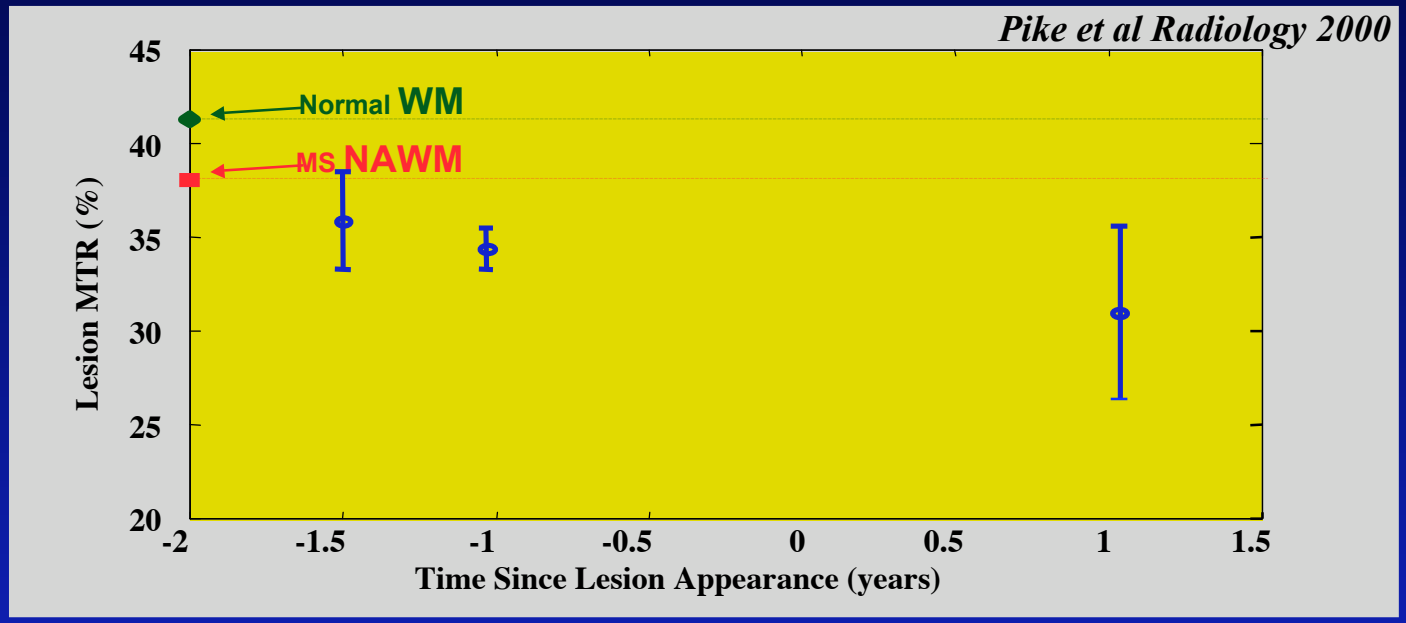


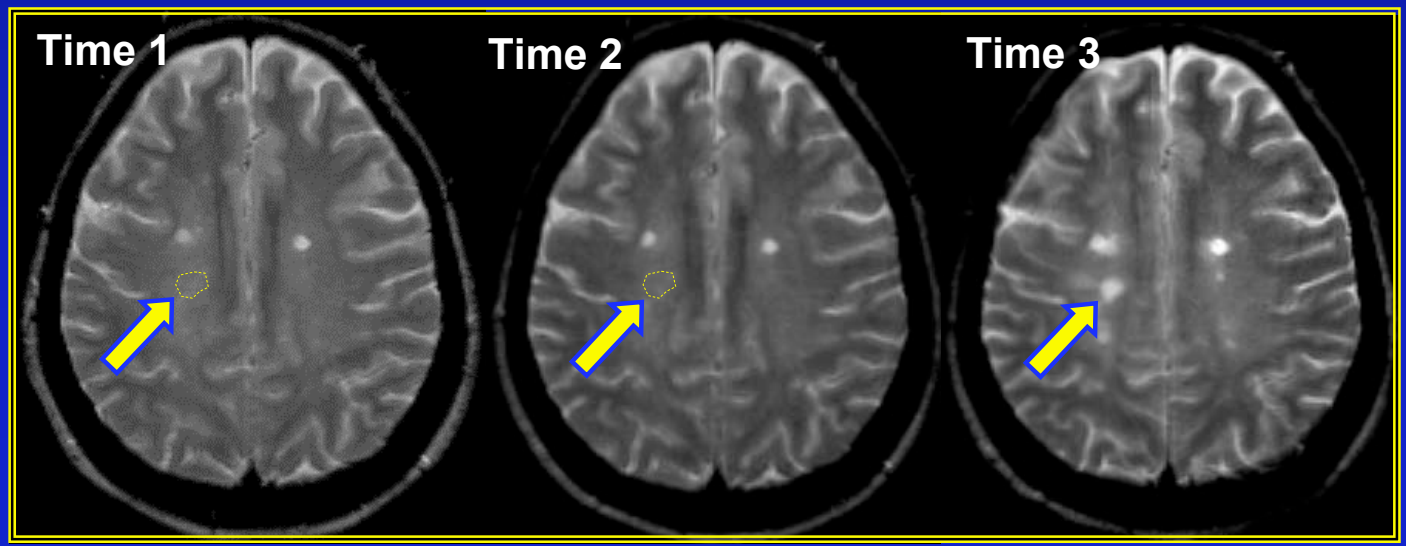
MTr & Axonal density



van Waesberghe et al., Ann Neurol 1999

Pre-Lesional-MTr in MS



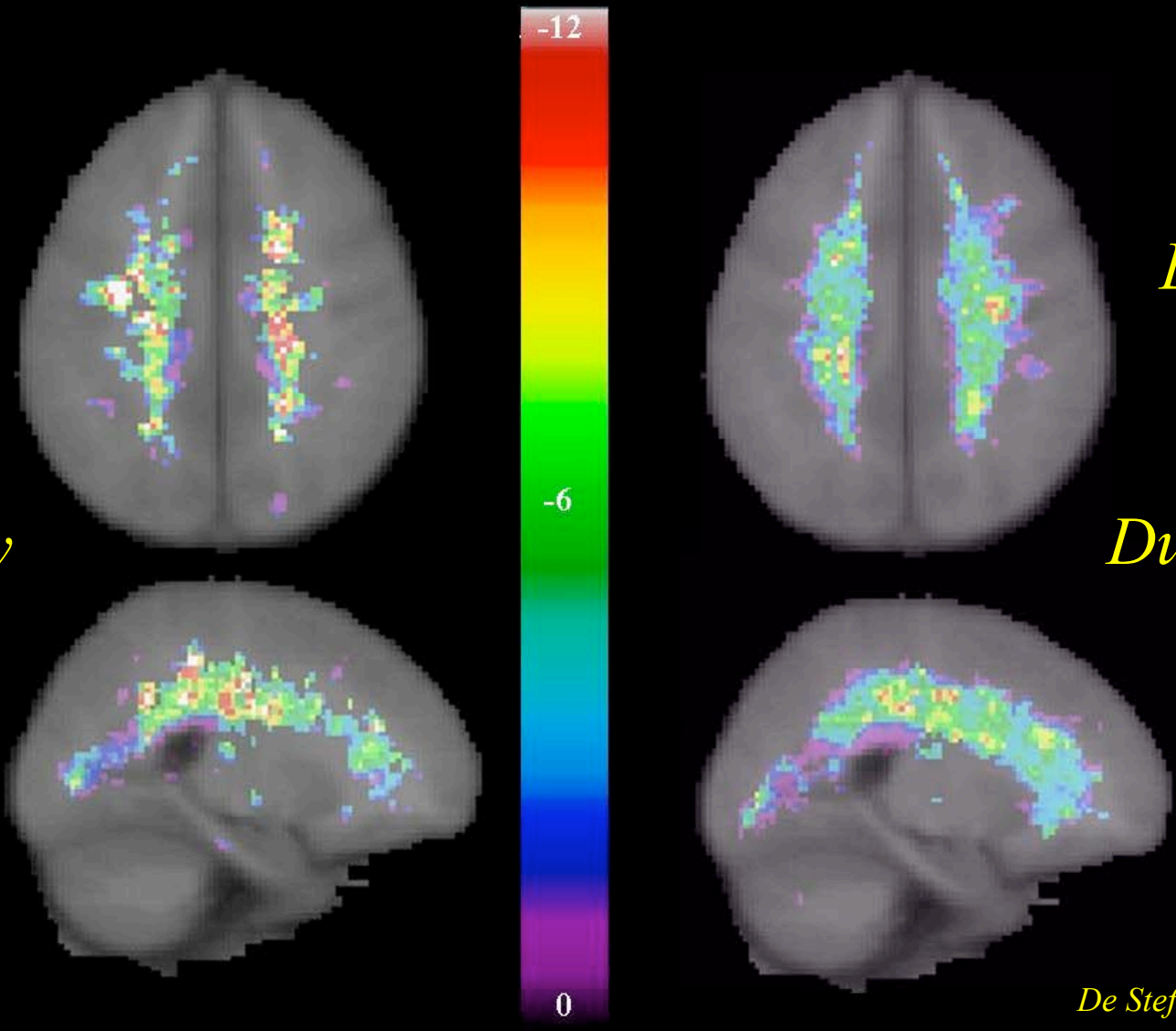


Voxel-Wise MTr in Lesions

50 Early RR & 50 Benign MS patients

Early RR

Duration <3y
EDSS <3



Benign MS

Duration >15y
EDSS <3

De Stefano et al ECTRIMS 2005

Multiple Sclerosis

MR measures of Neuro-Axonal Damage

- *T1-weighted WM lesions (Black Holes)*
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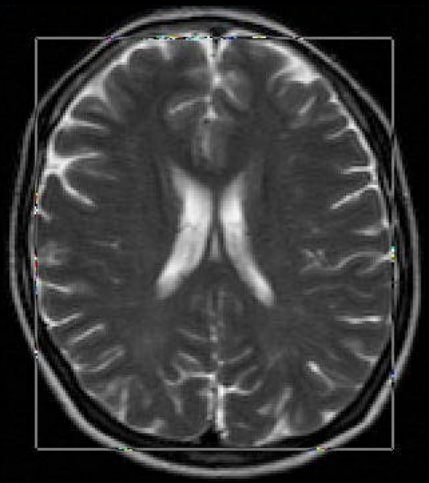
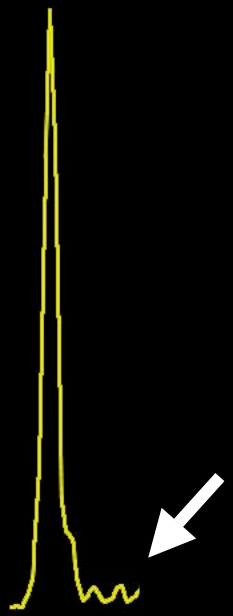
- *Brain Atrophy*

What is ^{1}H-MRS?

MR *Imaging* (*H_2O: 70 M*)





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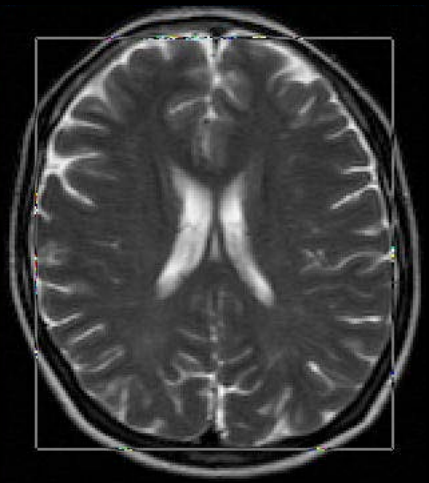
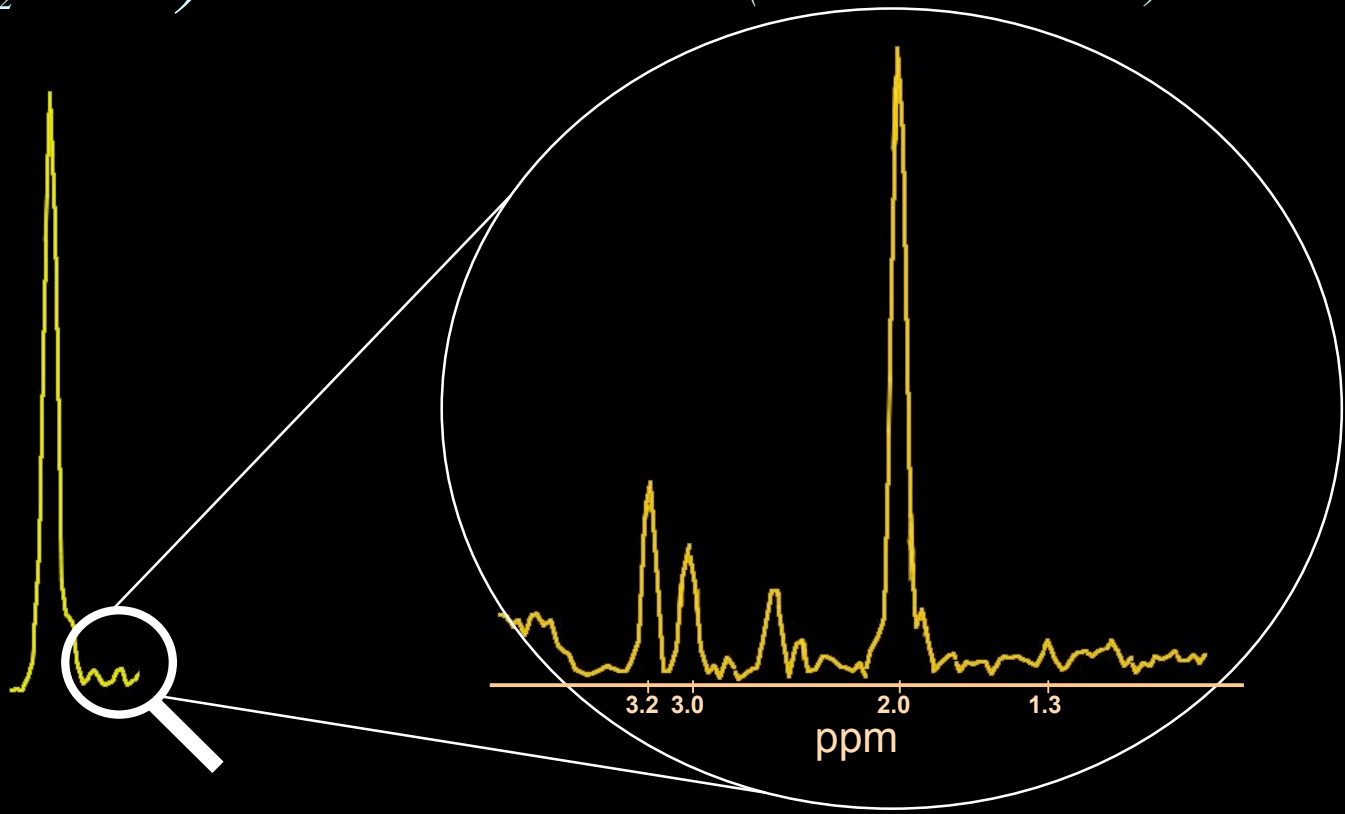
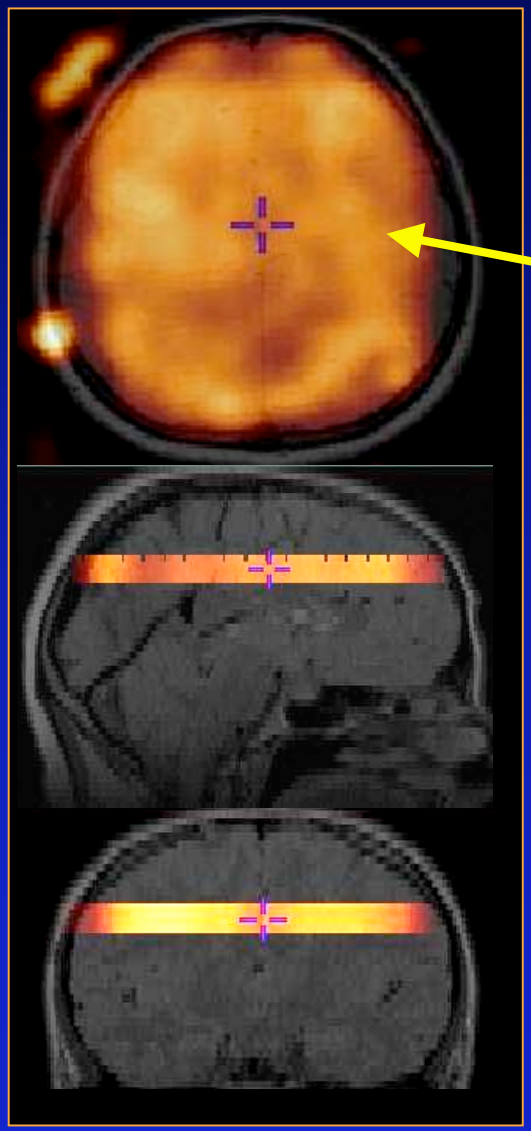


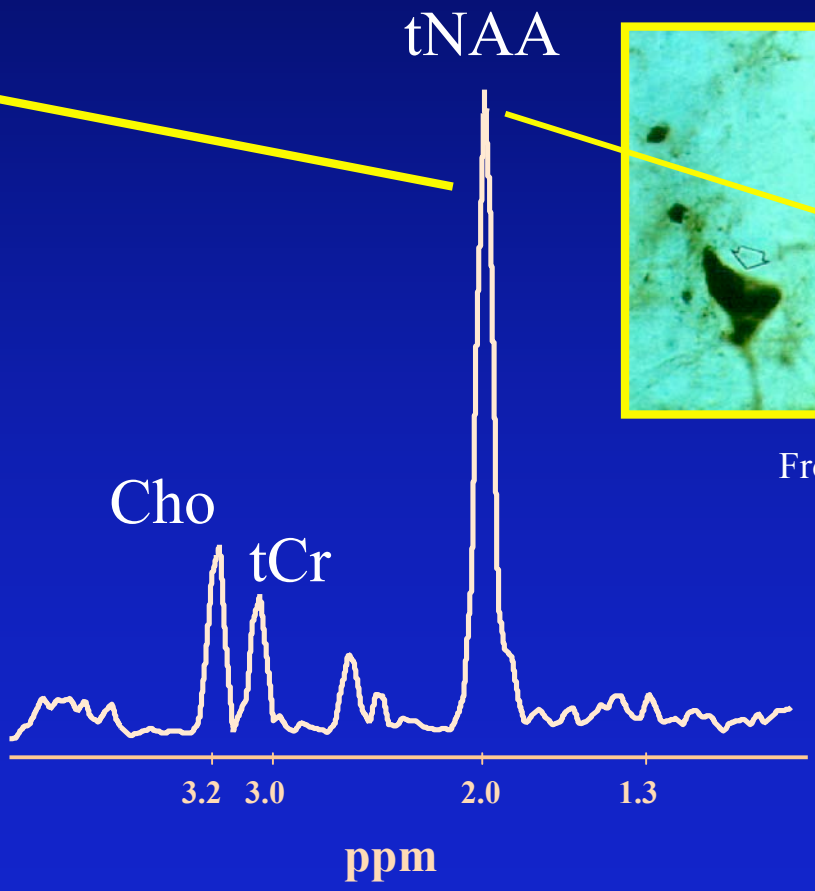
^{1}H-MRS *(metabolites: ~ 7mM)*

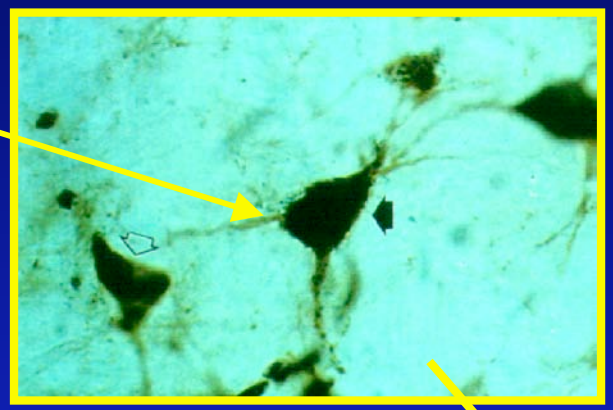


Proton MRS

Assessing Neuronal and Axonal Integrity in vivo





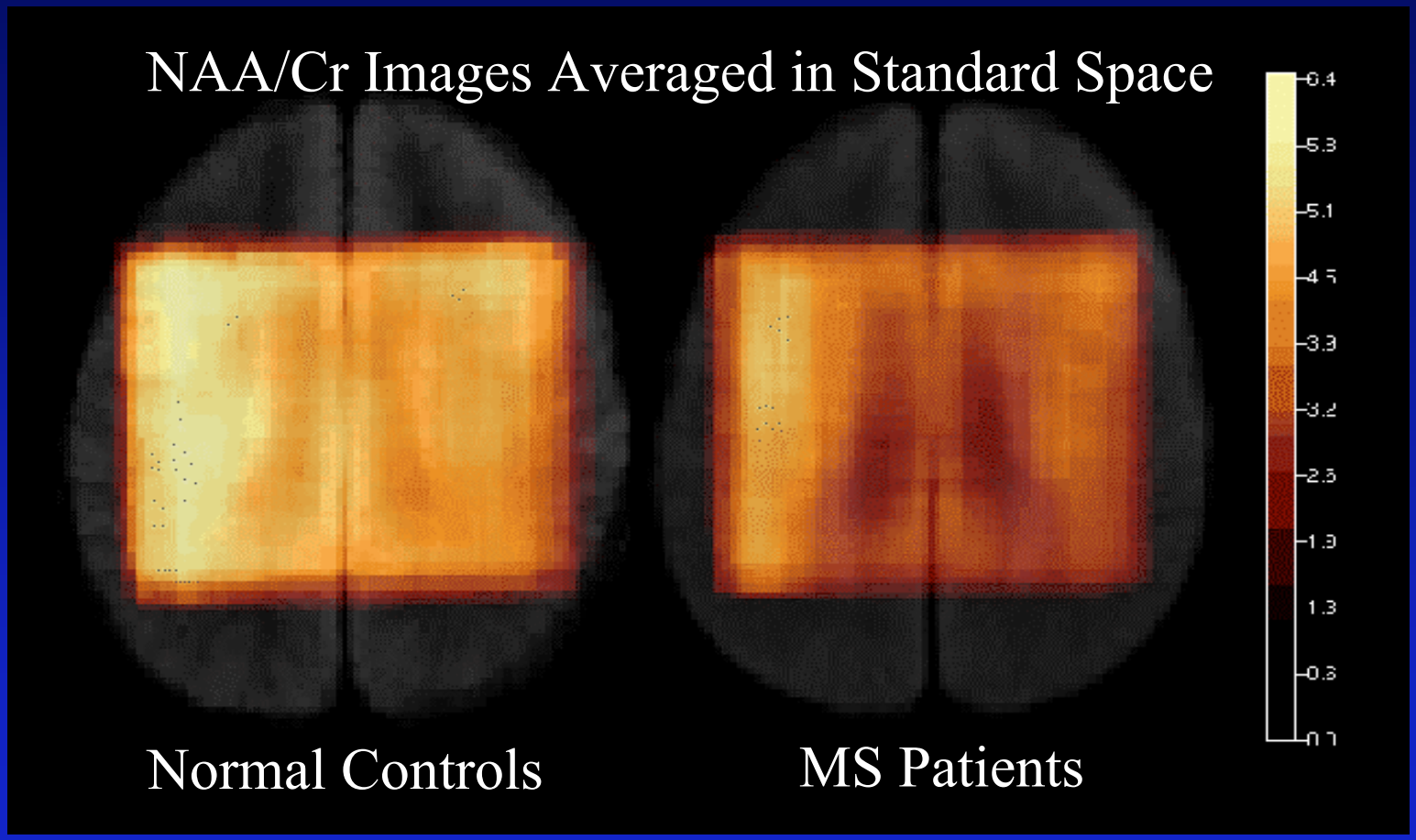


From Coyle, JT. (1989)

NAA decreases are due to axonal loss, damage, atrophy and potentially reversible axonal metabolic dysfunction

Widespread NAA Decrease

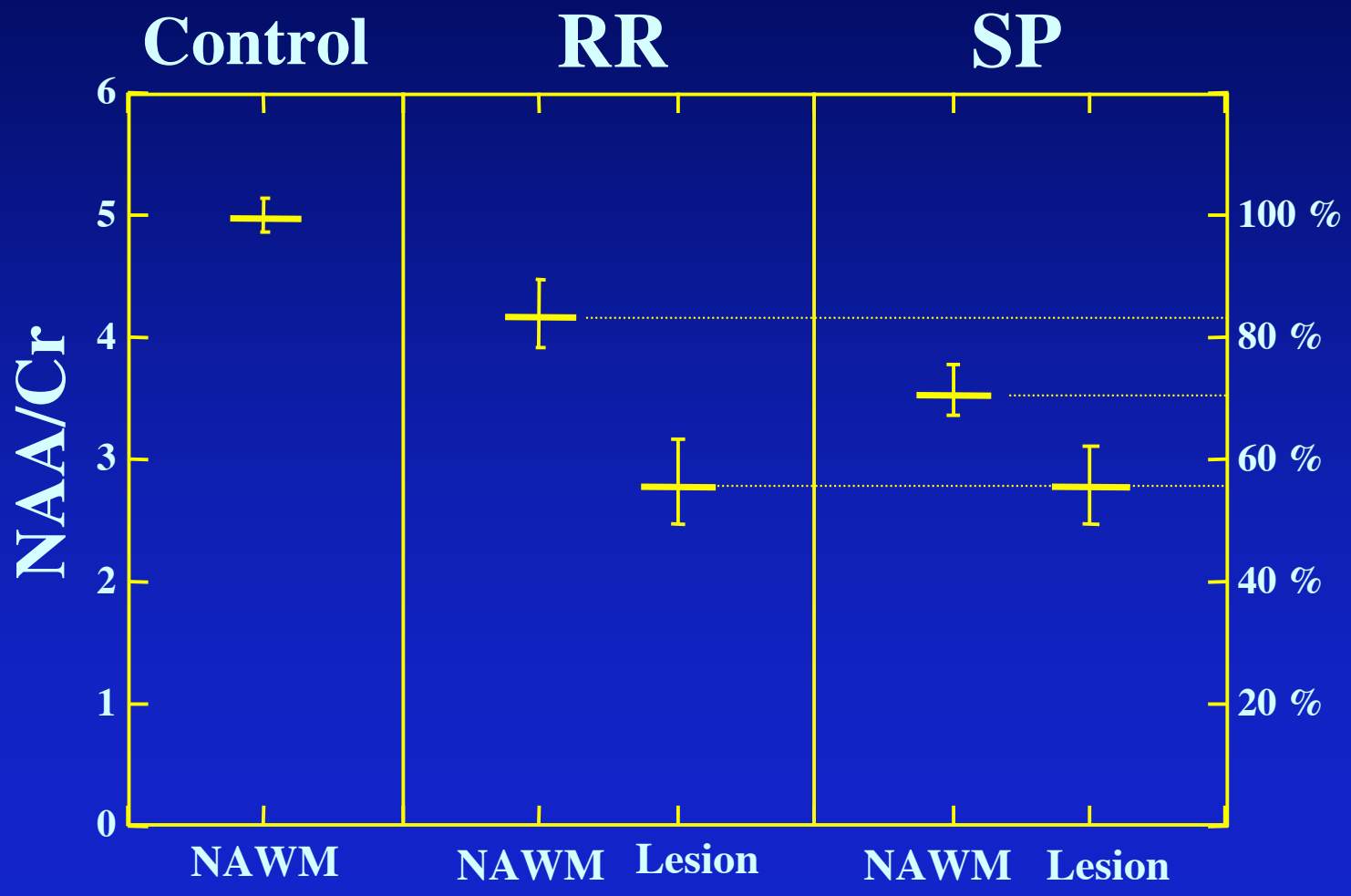
Axonal Damage Beyond Lesions



Narayanan et al., Ann Neurol 1997

Multiple Sclerosis

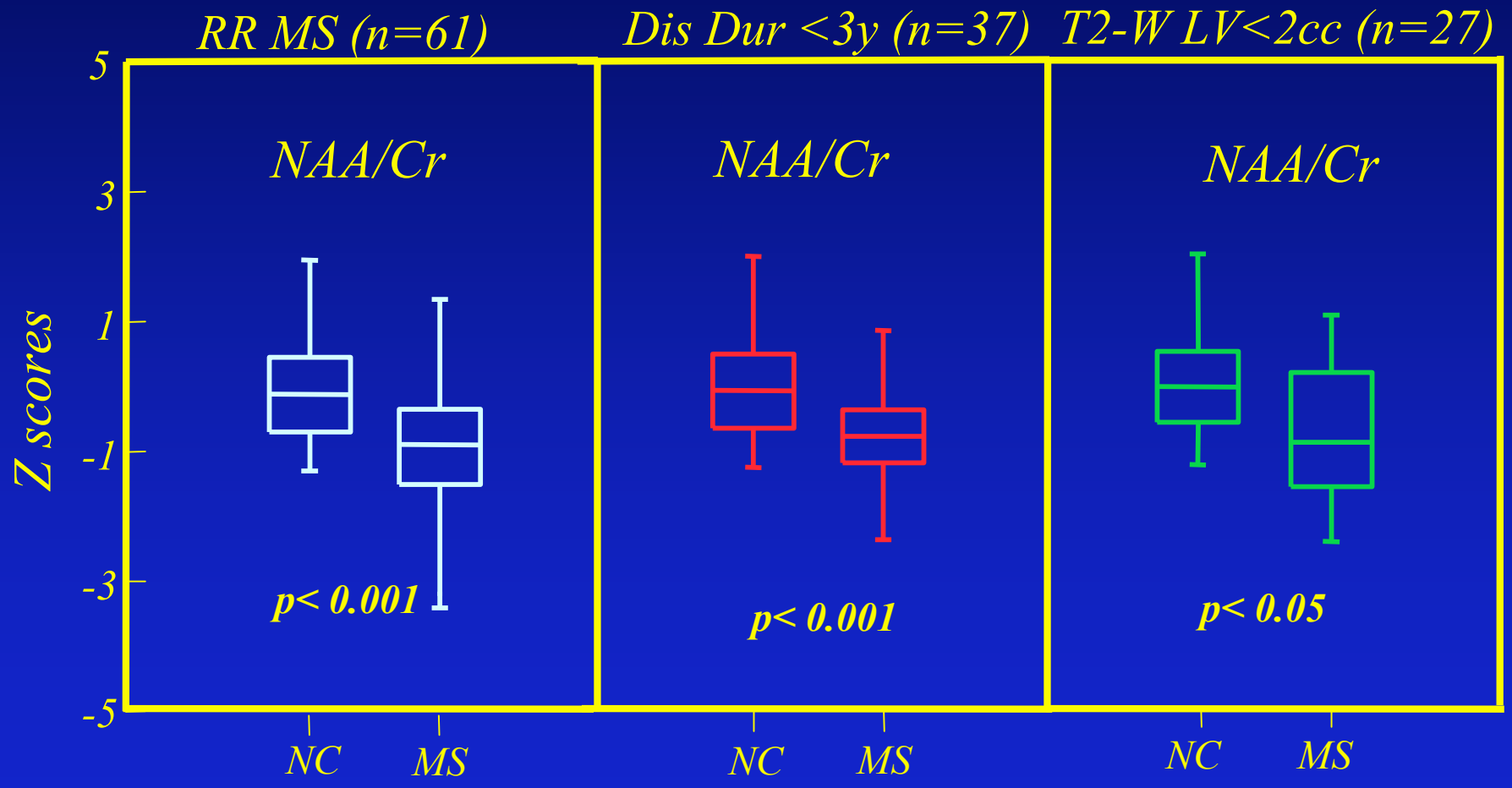
NAA/Cr in NAWM and lesions



Fu et al Brain 1998

Proton MRSI

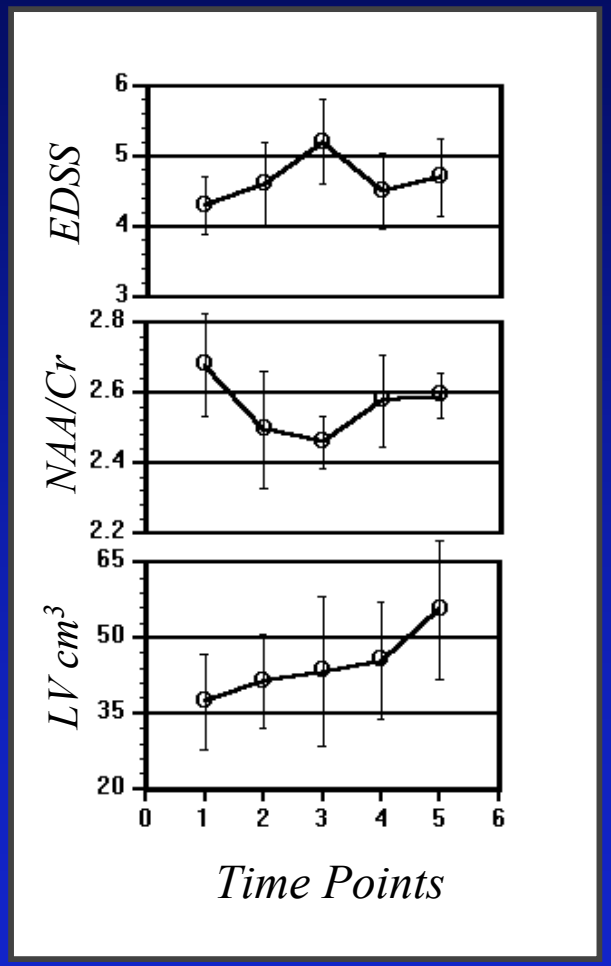
Non-Disabled MS patients Vs Normal Controls



De Stefano et al Arch Neurol 2002

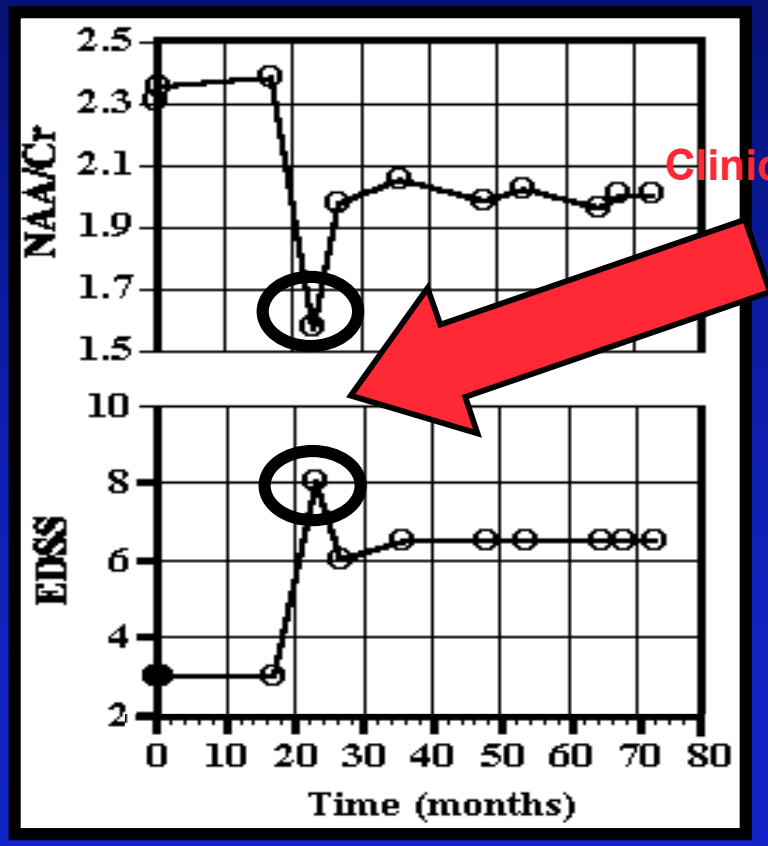
NAA & Disability

RR MS 30-month FU



De Stefano et al Brain 1998

1 Patient with MS



De Stefano et al Neurology 1997

Proton MRSI - Grey Matter *(From Chard et al Brain 2002)*

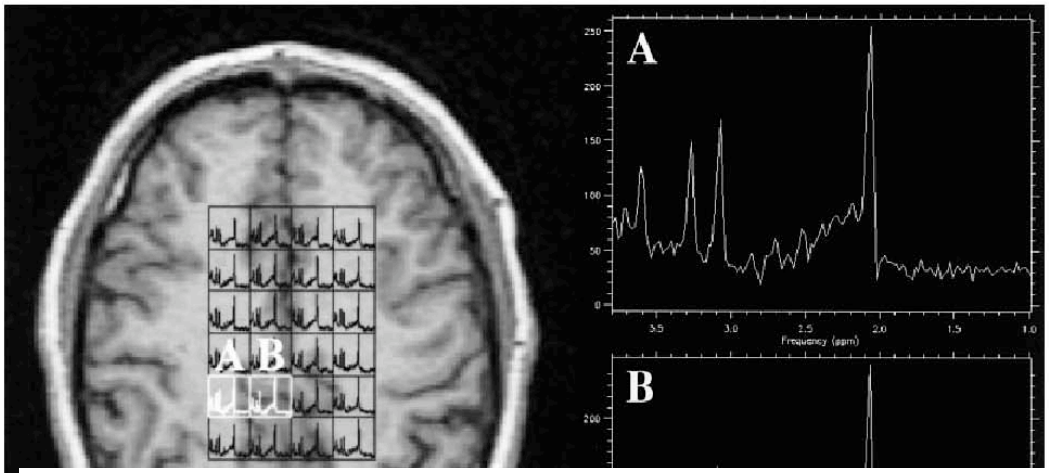


Table 4 *Multiple sclerosis disease effects estimated from multiple regression models*

Metabolite	Adjusted means (standard error) (mmol/l)[a]		Multiple sclerosis disease effects[b]		
	Normal control	Multiple sclerosis	Mean (standard error) (mmol/l)	Percentage effect[c]	*P* value
CGM Cho	1.188 (0.040)	1.009 (0.046)	–0.179 (0.063)	–15.1%	0.007
CGM Cr	6.239 (0.128)	5.917 (0.149)	–0.322 (0.203)	–5.2%	0.121
CGM Ins	4.482 (0.097)	4.333 (0.113)	–0.149 (0.154)	–3.3%	0.341
CGM tNAA	8.897 (0.149)	8.312 (0.173)	–0.585 (0.237)	–6.6%	0.018
CGM Glx	12.210 (0.293)	11.111 (0.340)	–1.099 (0.465)	–9.0%	0.023
NAWM Cho	1.289 (0.34)	1.216 (0.38)	–0.072 (0.052)	–5.6%	0.167
NAWM Cr	4.917 (0.76)	4.871 (0.084)	–0.046 (0.115)	–0.9%	0.690
NAWM Ins	3.689 (0.097)	4.089 (0.107)	+0.400 (0.146)	+10.8%	0.009
NAWM tNAA	8.781 (0.128)	8.350 (0.142)	–0.431 (0.194)	–4.9%	0.031
NAWM Glx	7.750 (0.141)	7.823 (0.156)	+0.073 (0.213)	+0.9%	0.735

Multiple Sclerosis

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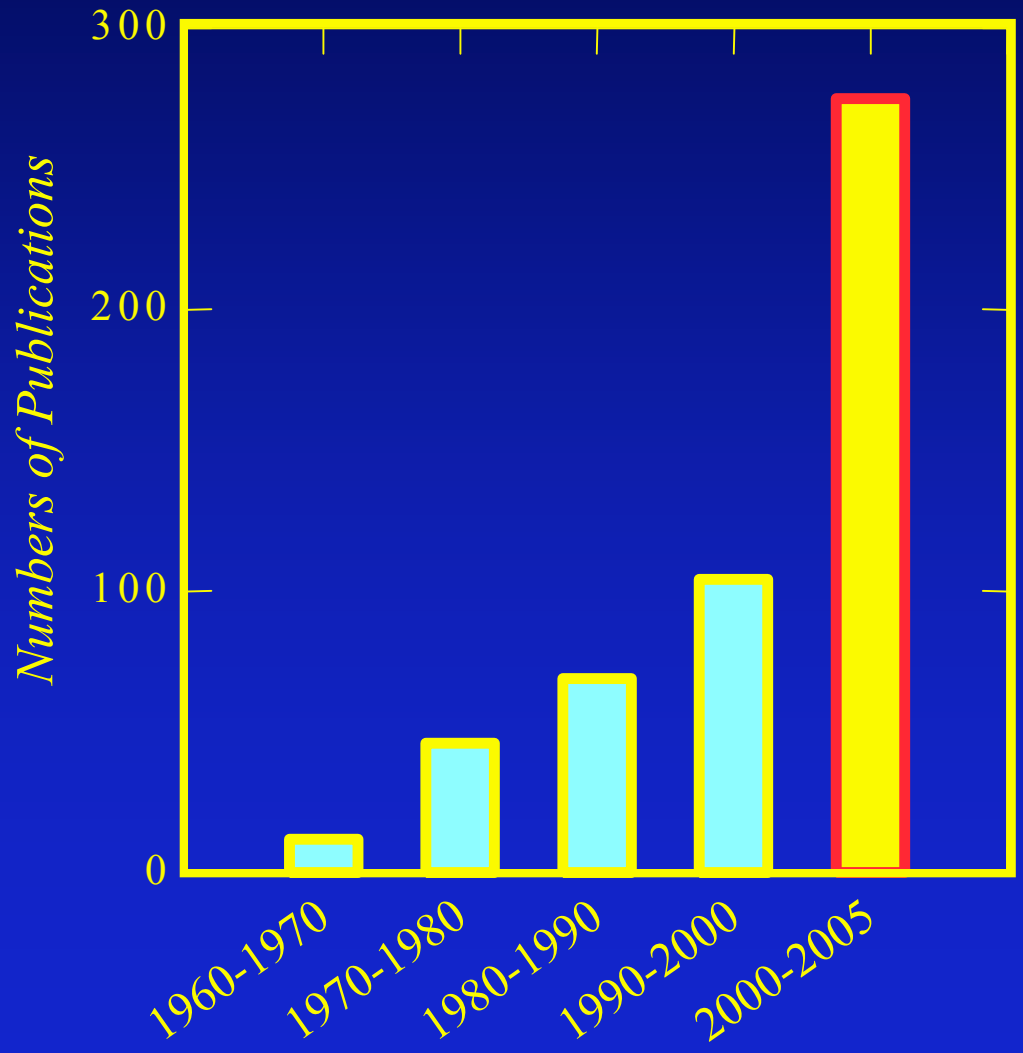
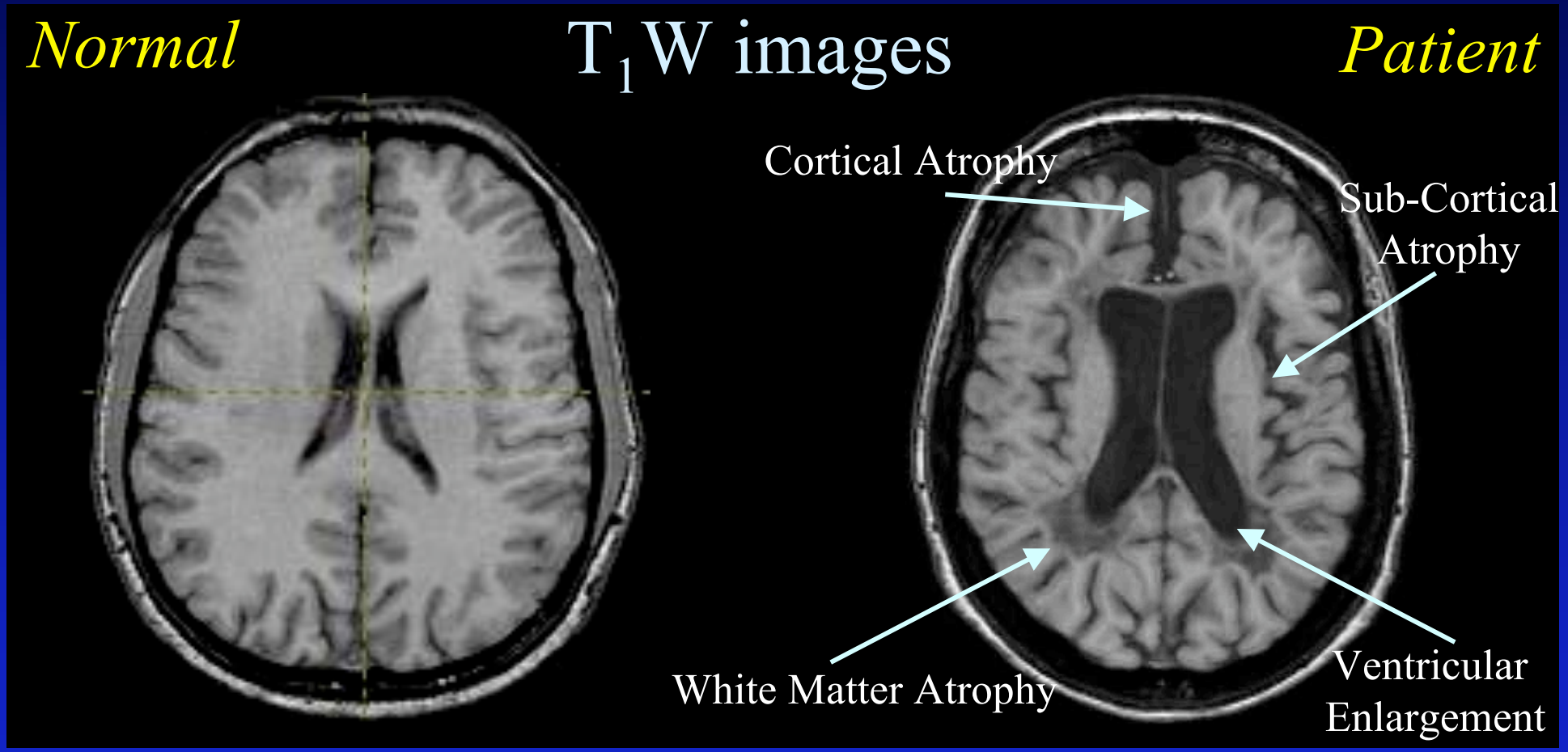
Brain Atrophy & Multiple Sclerosis

Scientific Publications



What is Brain Atrophy

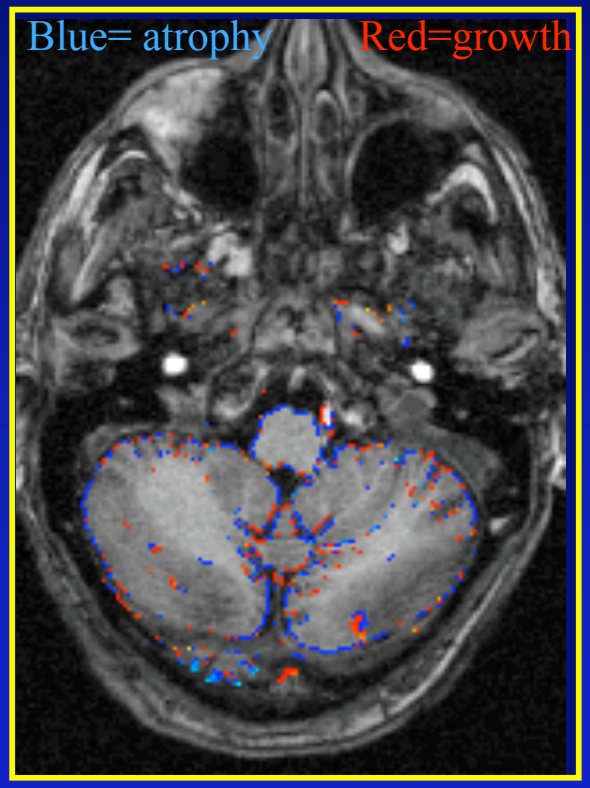


Brain Atrophy

Structural Image Evaluation of Normalised Atrophy

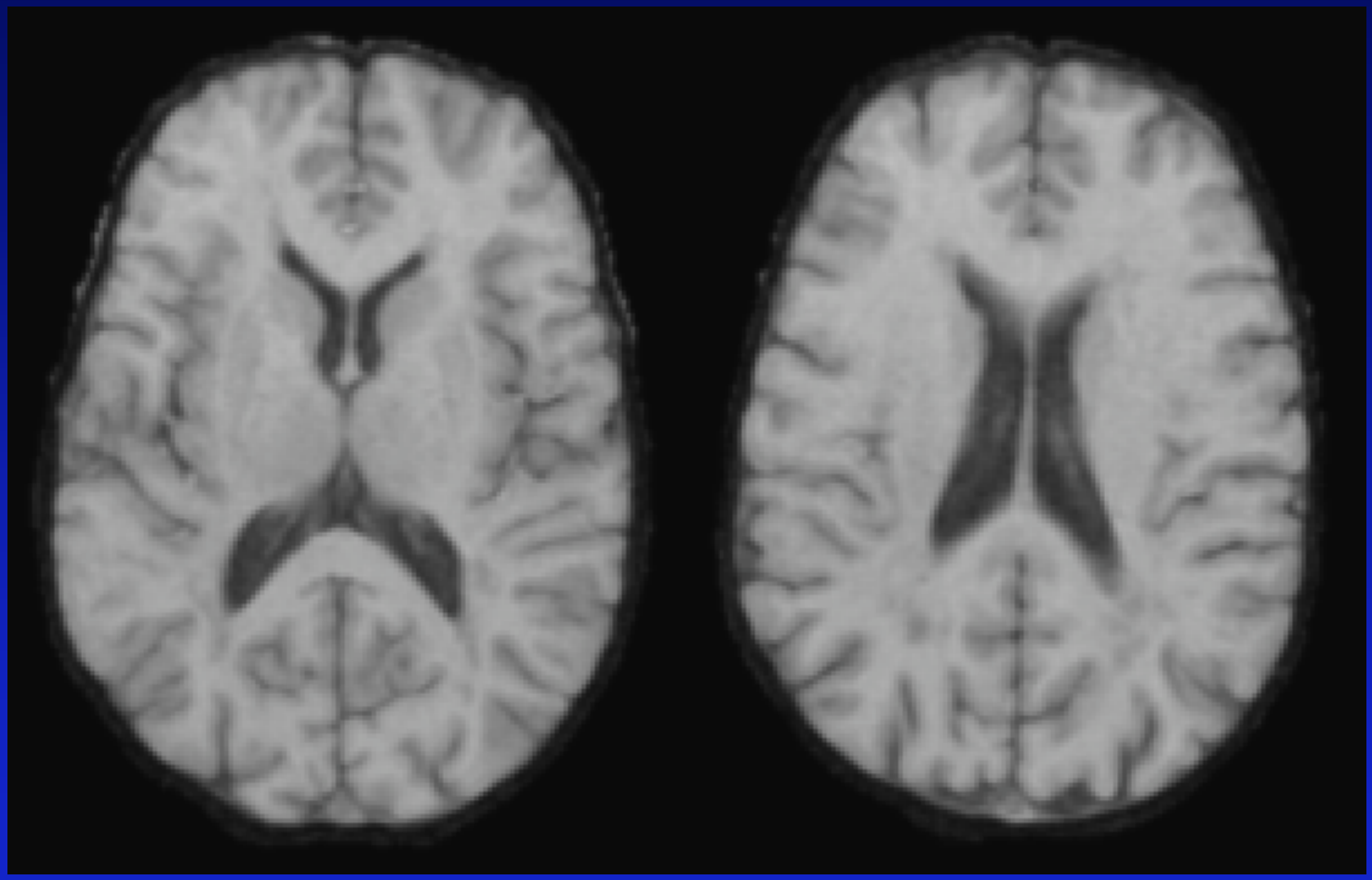
SIENAX

SIENA



- *Longitudinal, Cross Sectional & Regional*
- *Accurate and fully automatic*
- *Measures atrophy & brain change*
- *Proven for a range of slice thickness*
- *Proven for a range of MRI sequences*
- *Correction for scanner geometry drifts*
- *Accuracy 0.2-0.5% of brain volume*

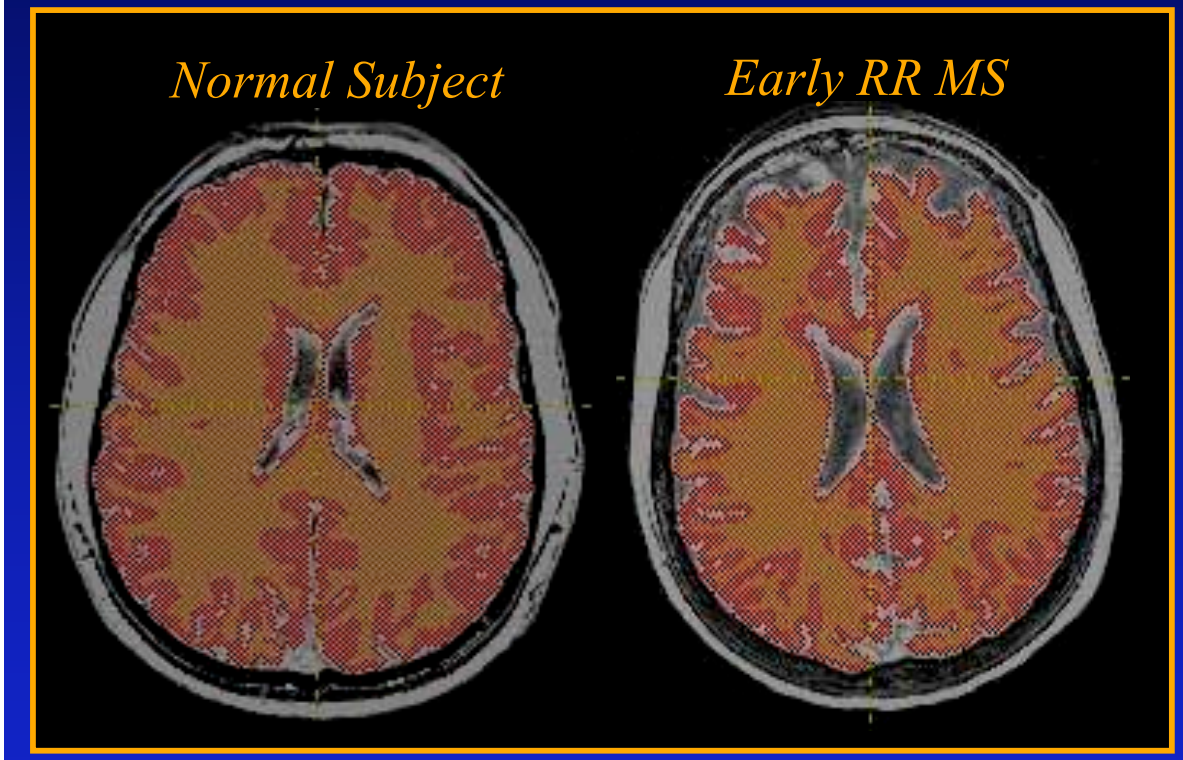
Example of Atrophy in Action

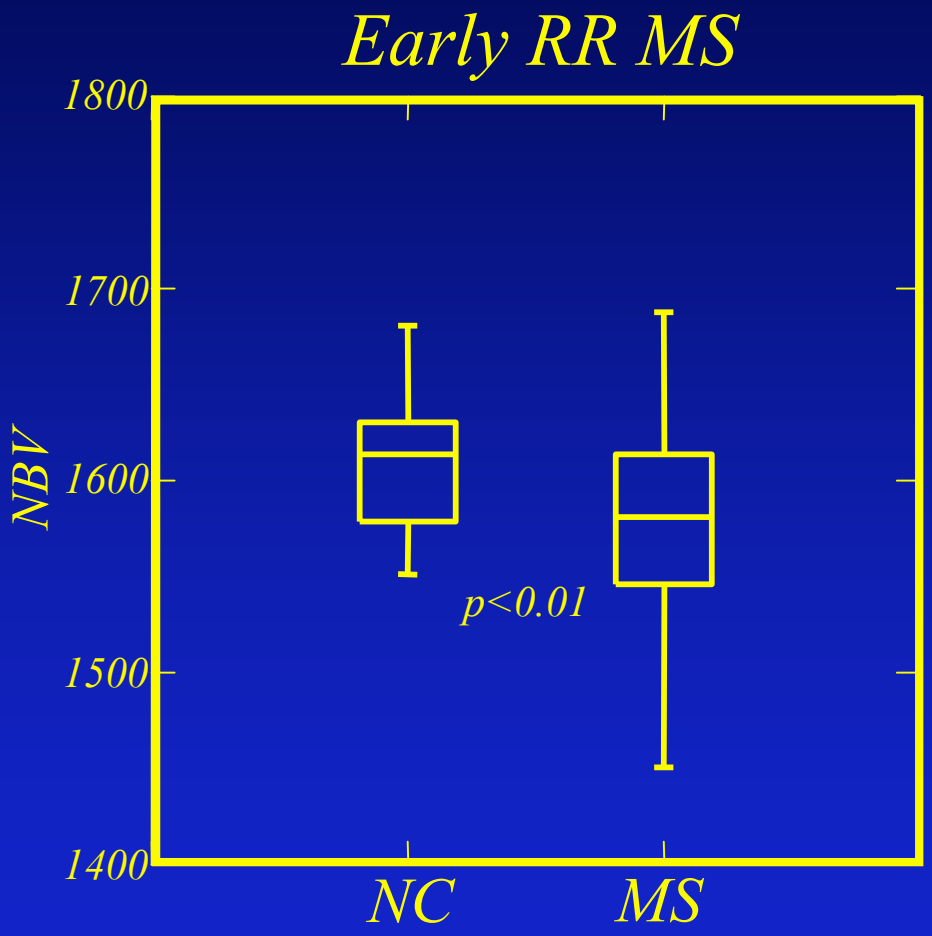


1 MS patient: Differences in 1 year

Early Brain Atrophy in MS

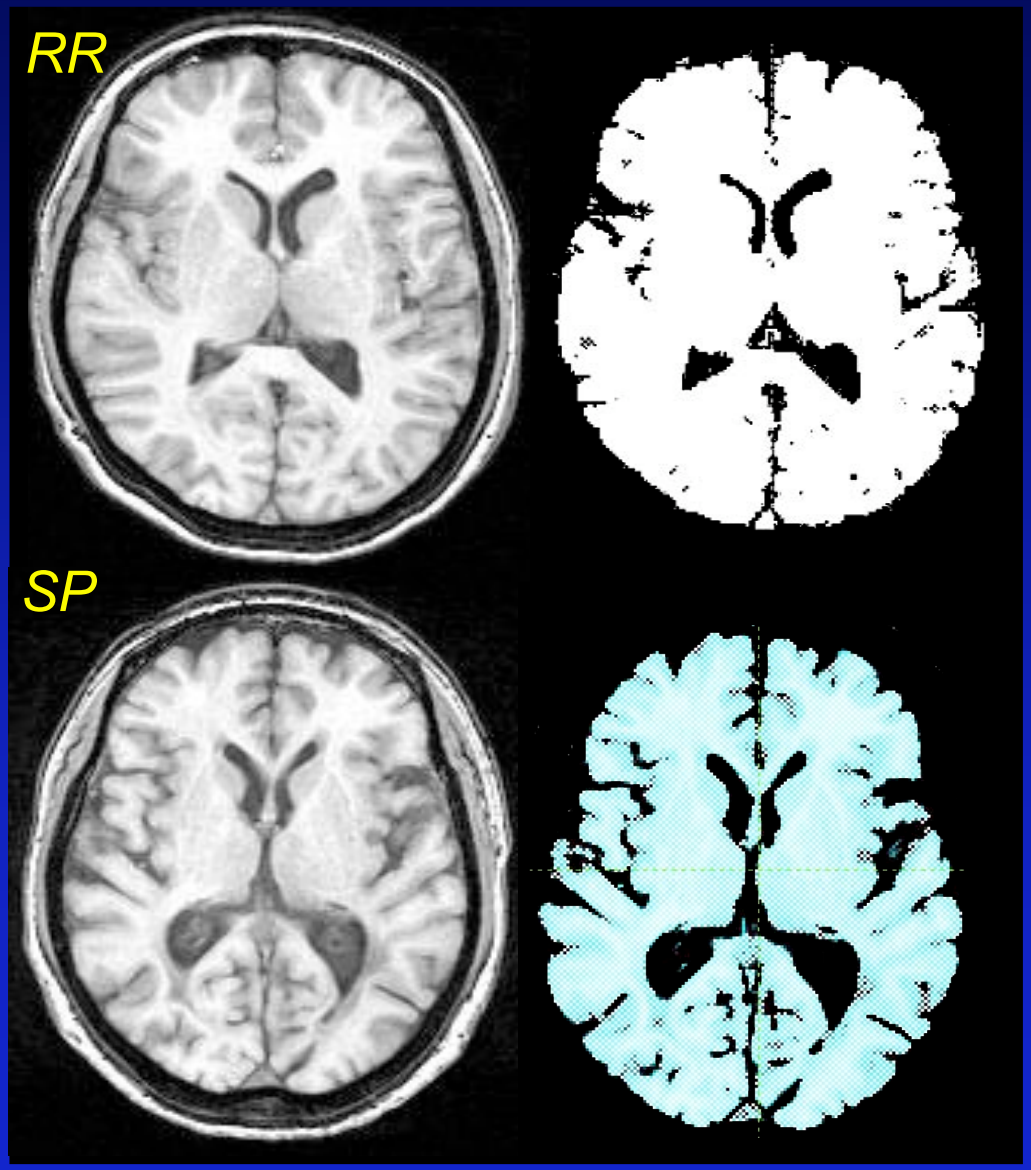
22 Normal Controls vs 76 RR MS

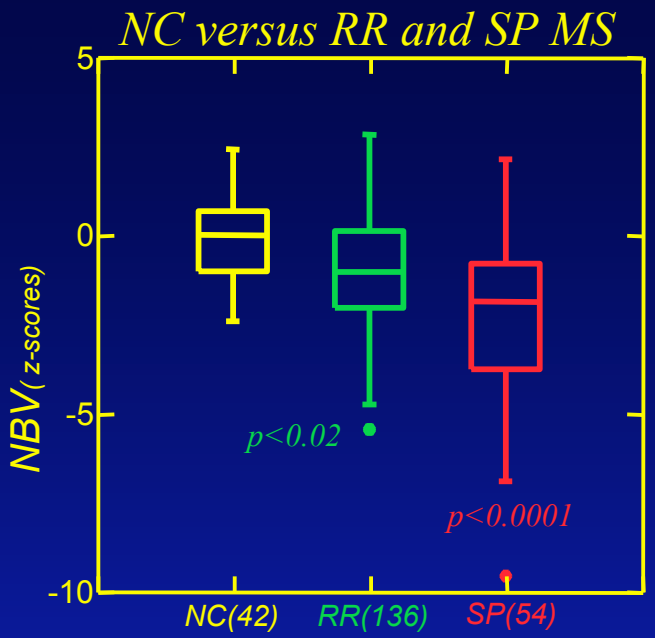




Brain Atrophy in MS

RR versus SP





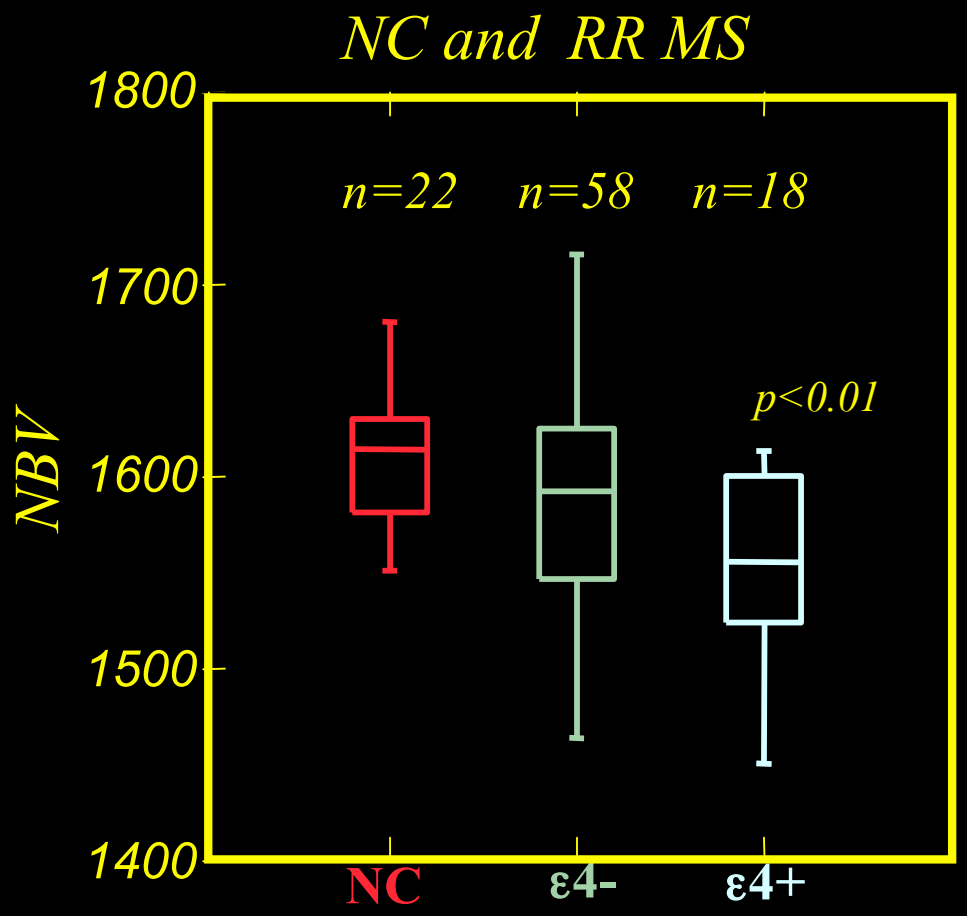
Brain Atrophy

SP > RR

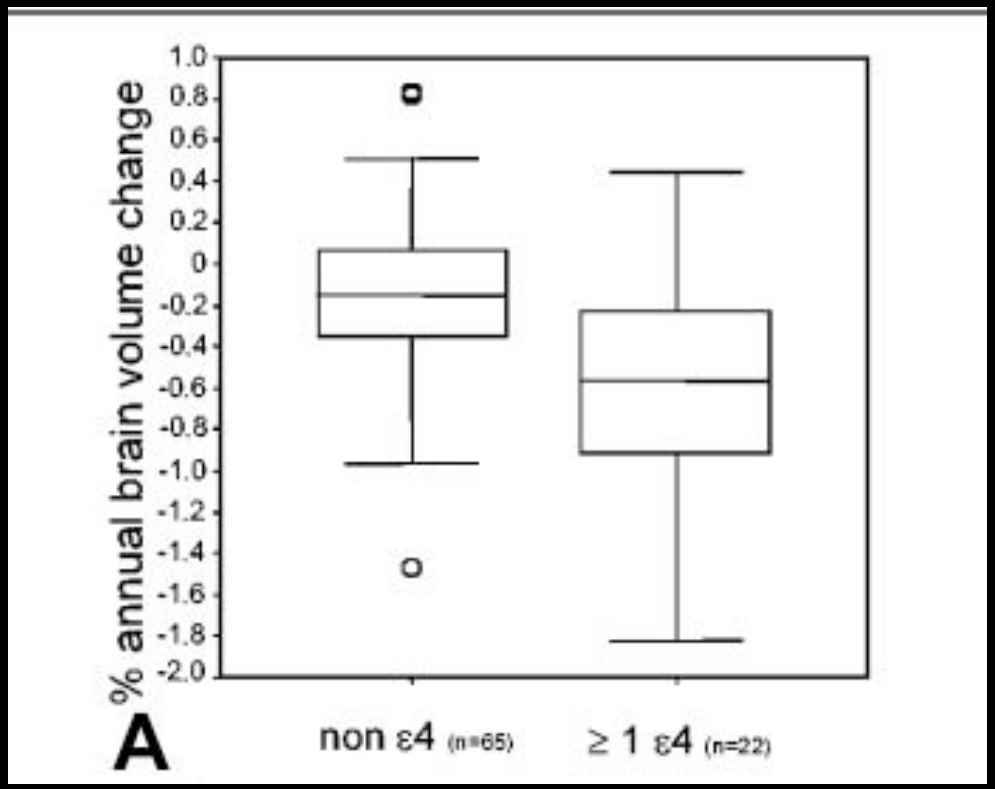
- **Disease Duration?**
- **Disease Severity?**

Brain Atrophy in MS

Influence of ApoE Genotype



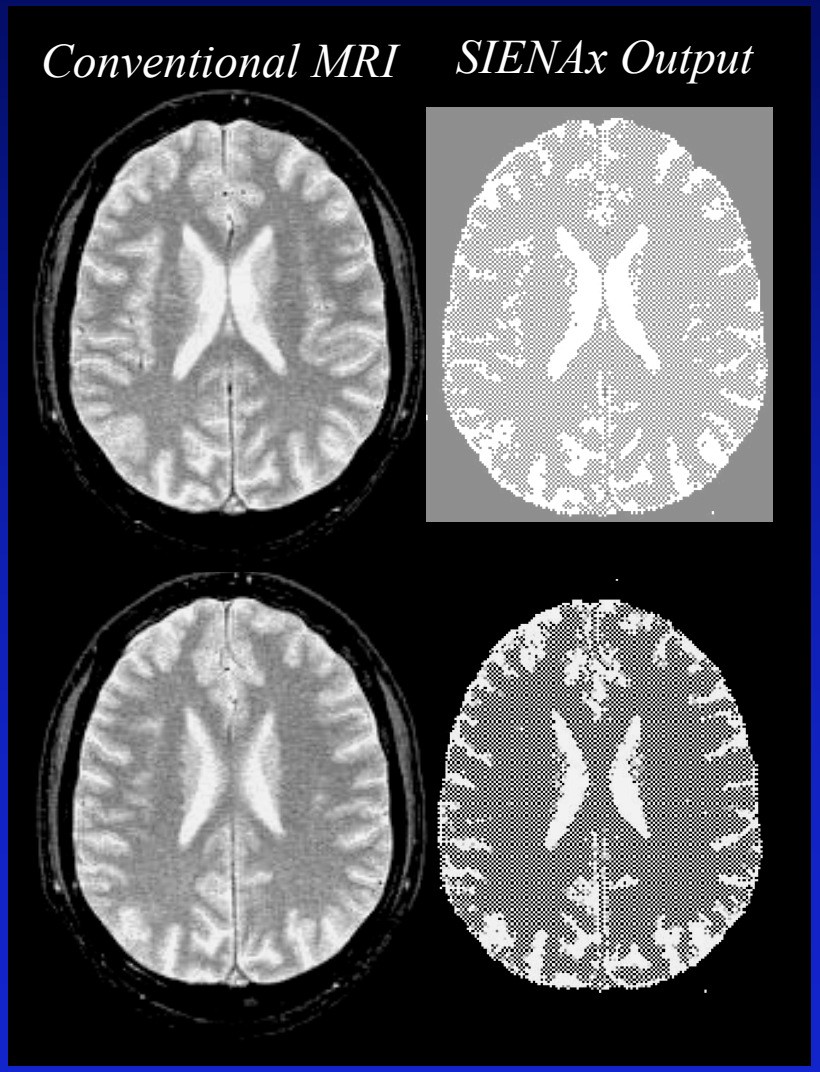
De Stefano et al., Arch Neurol 2004

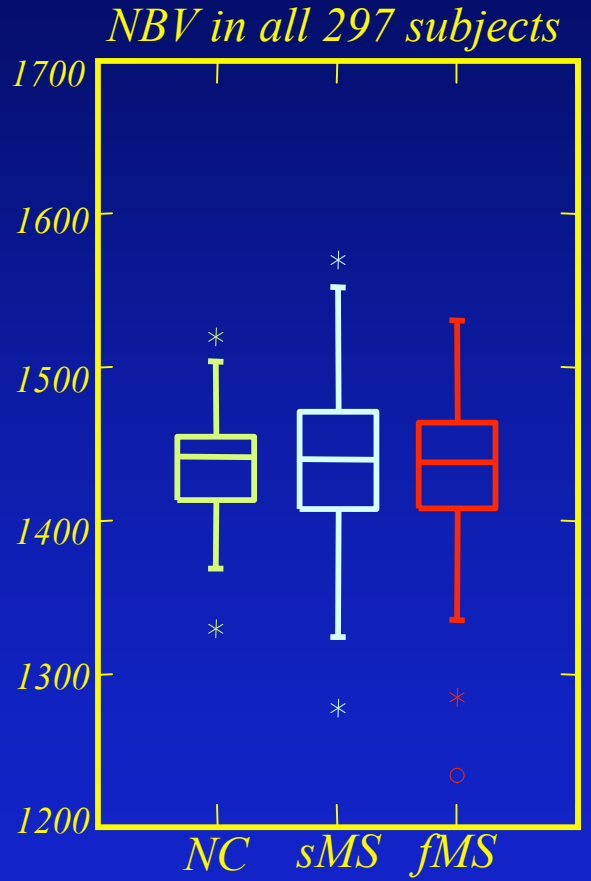


Enzinger et al., Ann Neurol 2004

NBV in Asymptomatic First-Degree MS relatives

56 NC, 153 sMS and 88 fMS

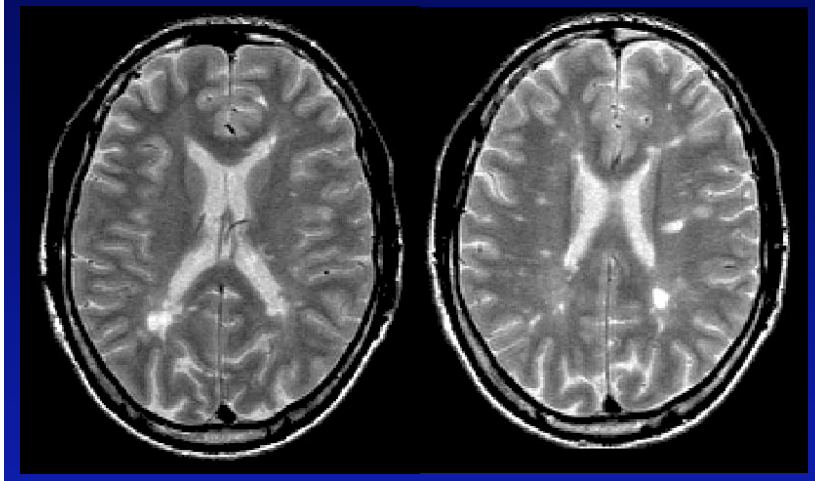


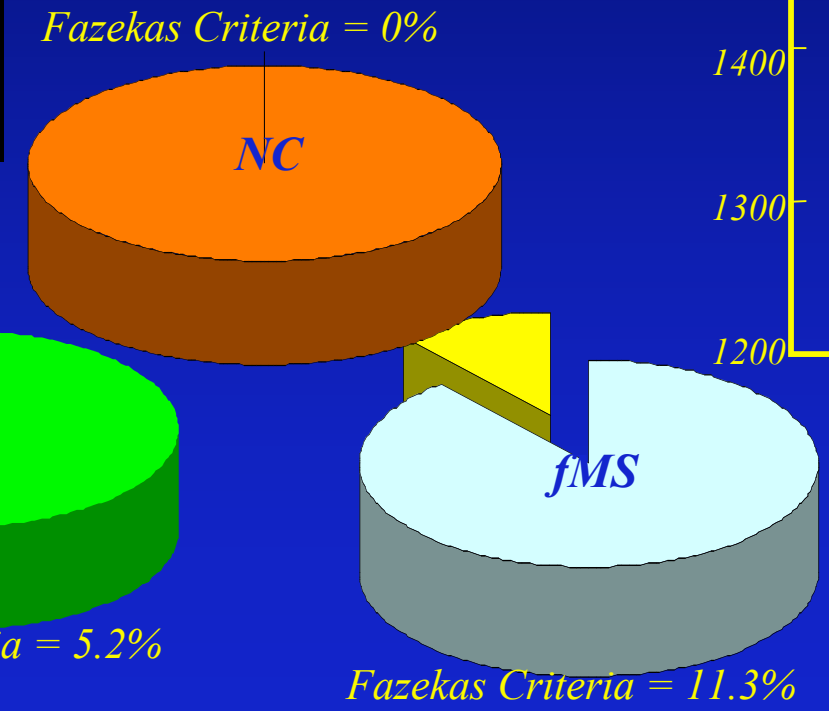


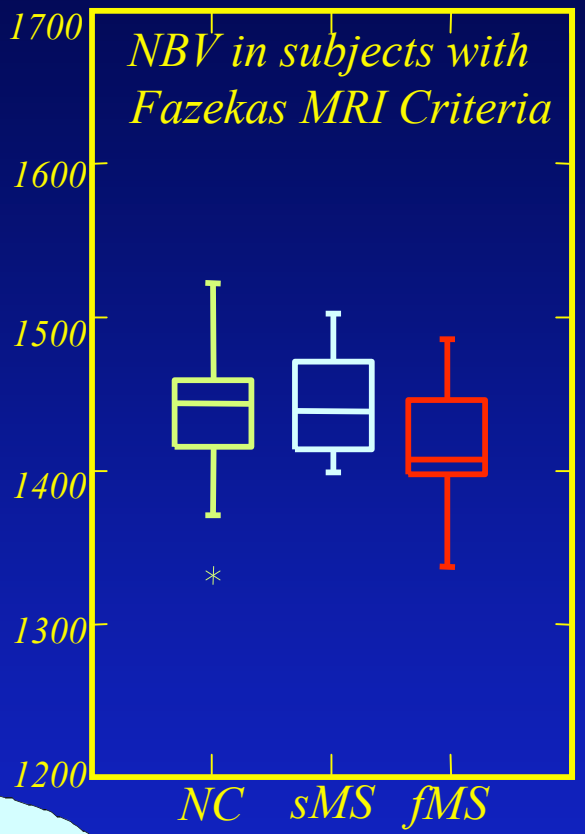
De Stefano et al., Ann Neurol 2006

NBV in Asymptomatic First-Degree MS relatives

MRI meeting Fazekas Criteria

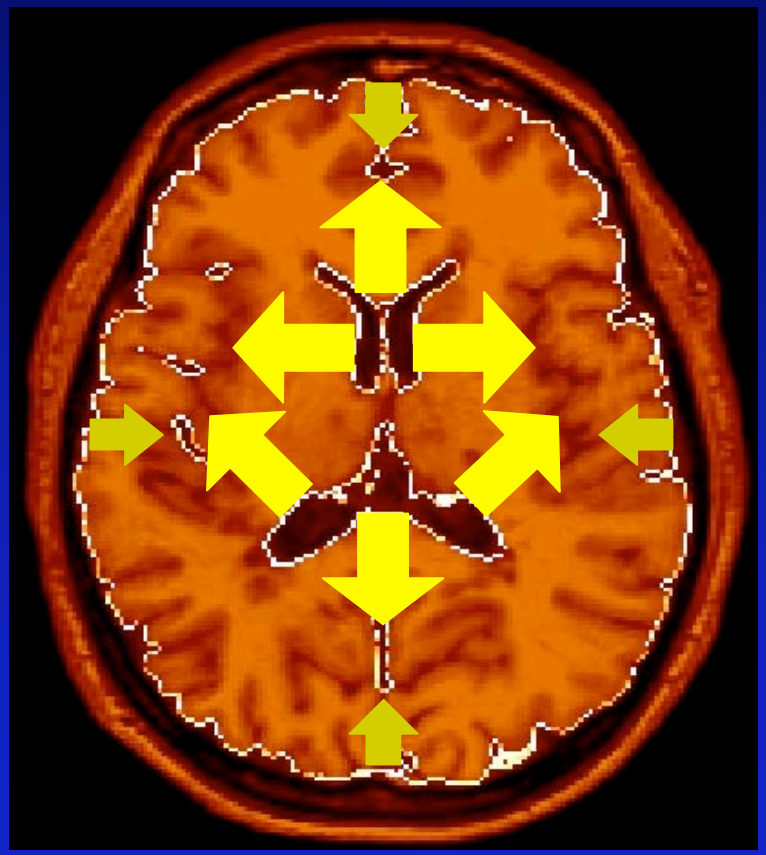




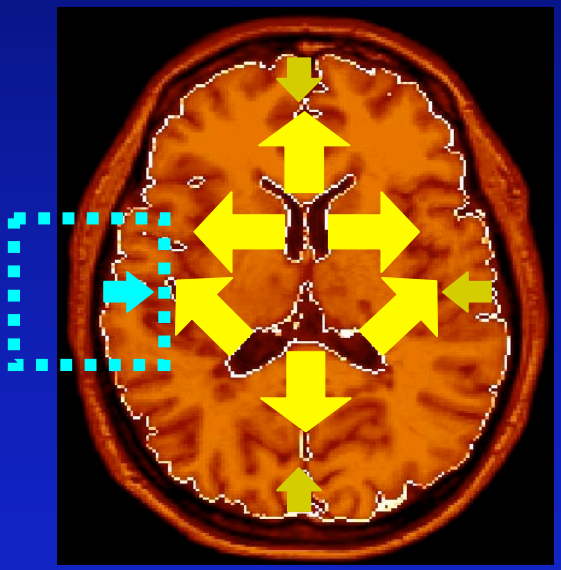


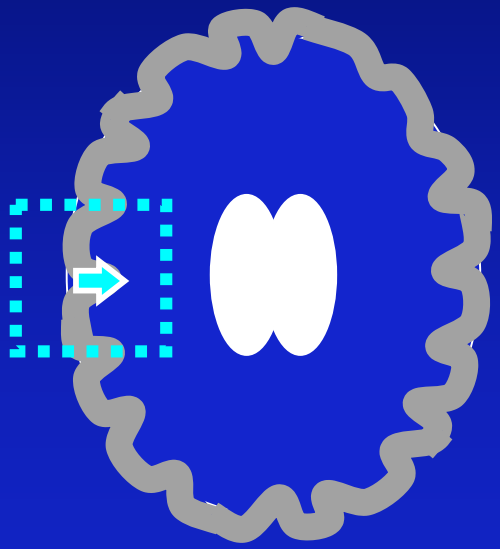
De Stefano et al., Ann Neurol 2006

Brain Atrophy in MS

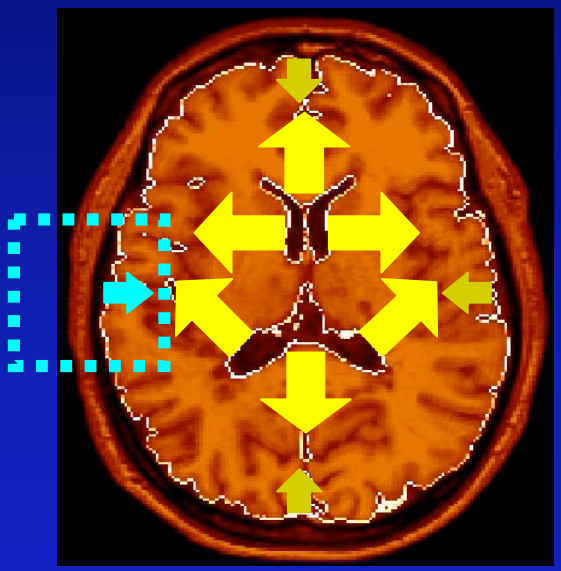


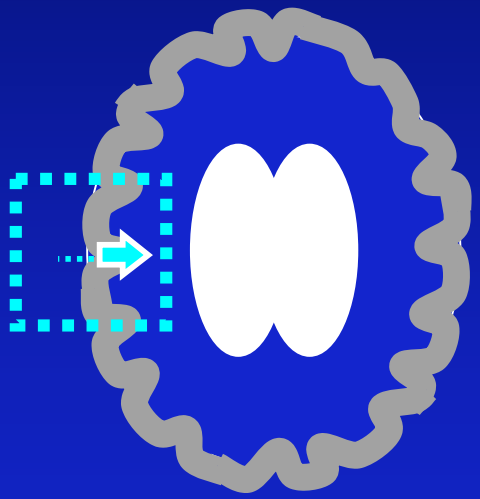
Brain Atrophy in MS



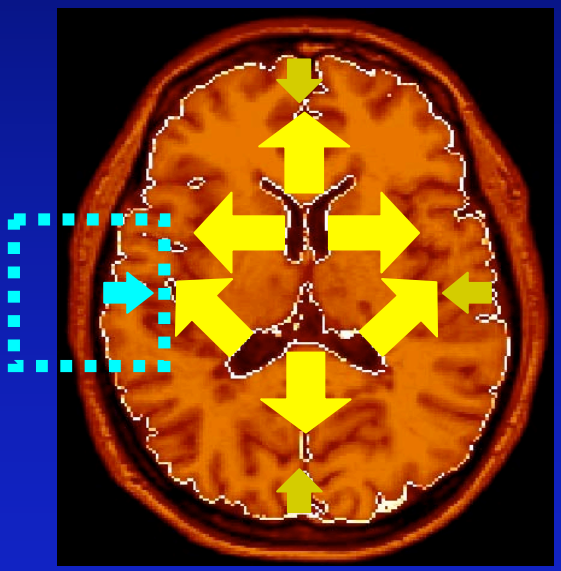


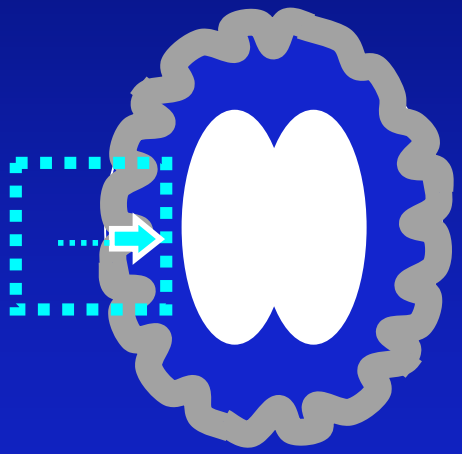
Brain Atrophy in MS





Brain Atrophy in MS

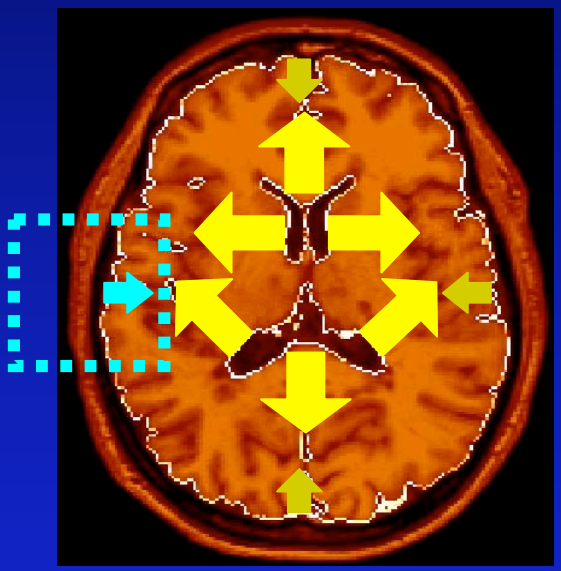


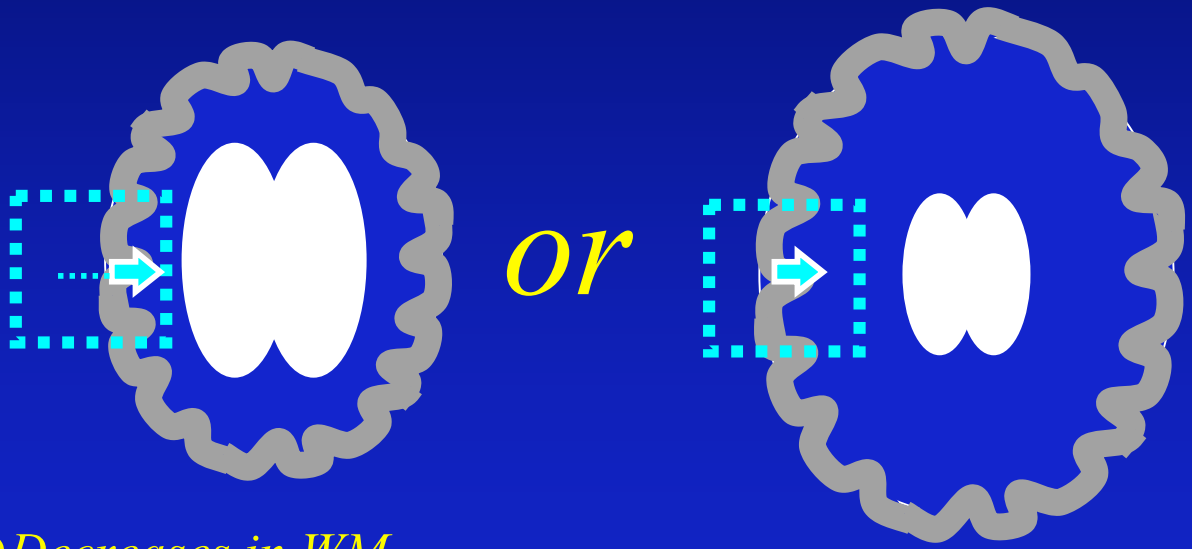


or

- *Decreases in WM*
- *Increases in Lateral Ventricles*

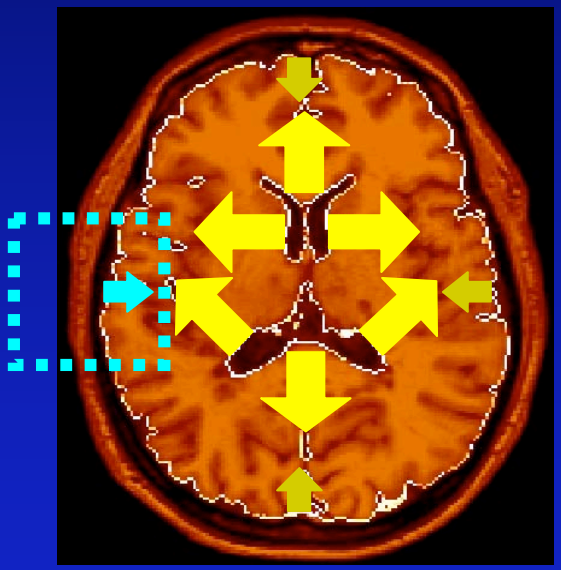
Brain Atrophy in MS

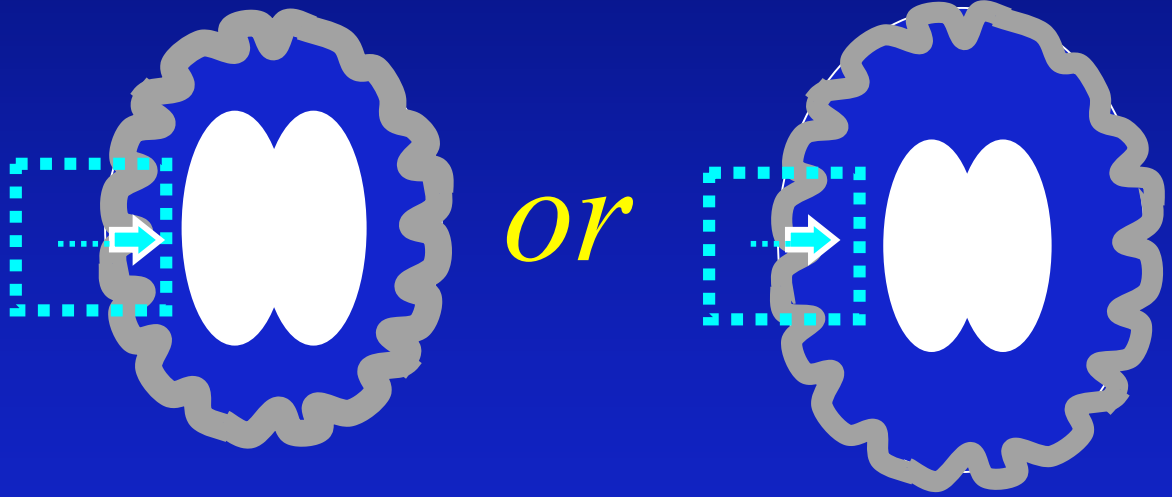




- *Decreases in WM*
- *Increases in Lateral Ventricles*

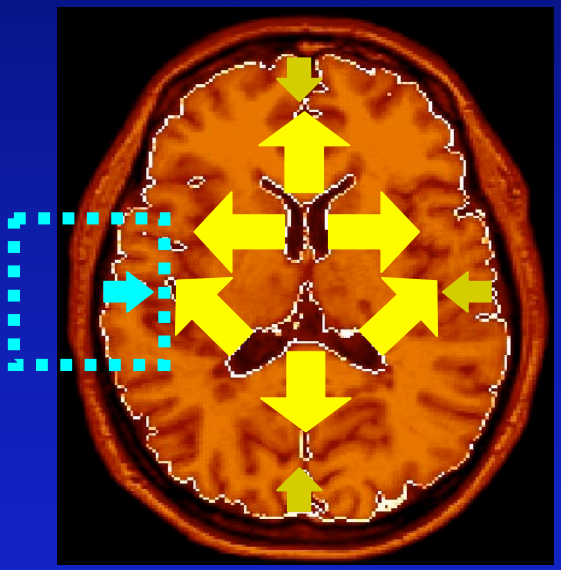
Brain Atrophy in MS

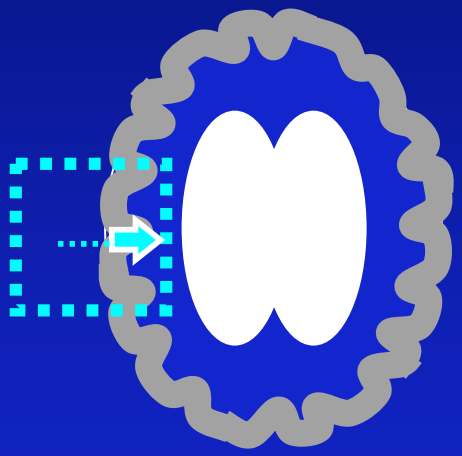




- *Decreases in WM*
- *Increases in Lateral Ventricles*

Brain Atrophy in MS





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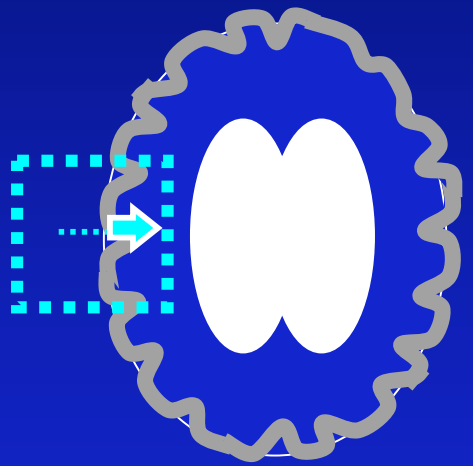
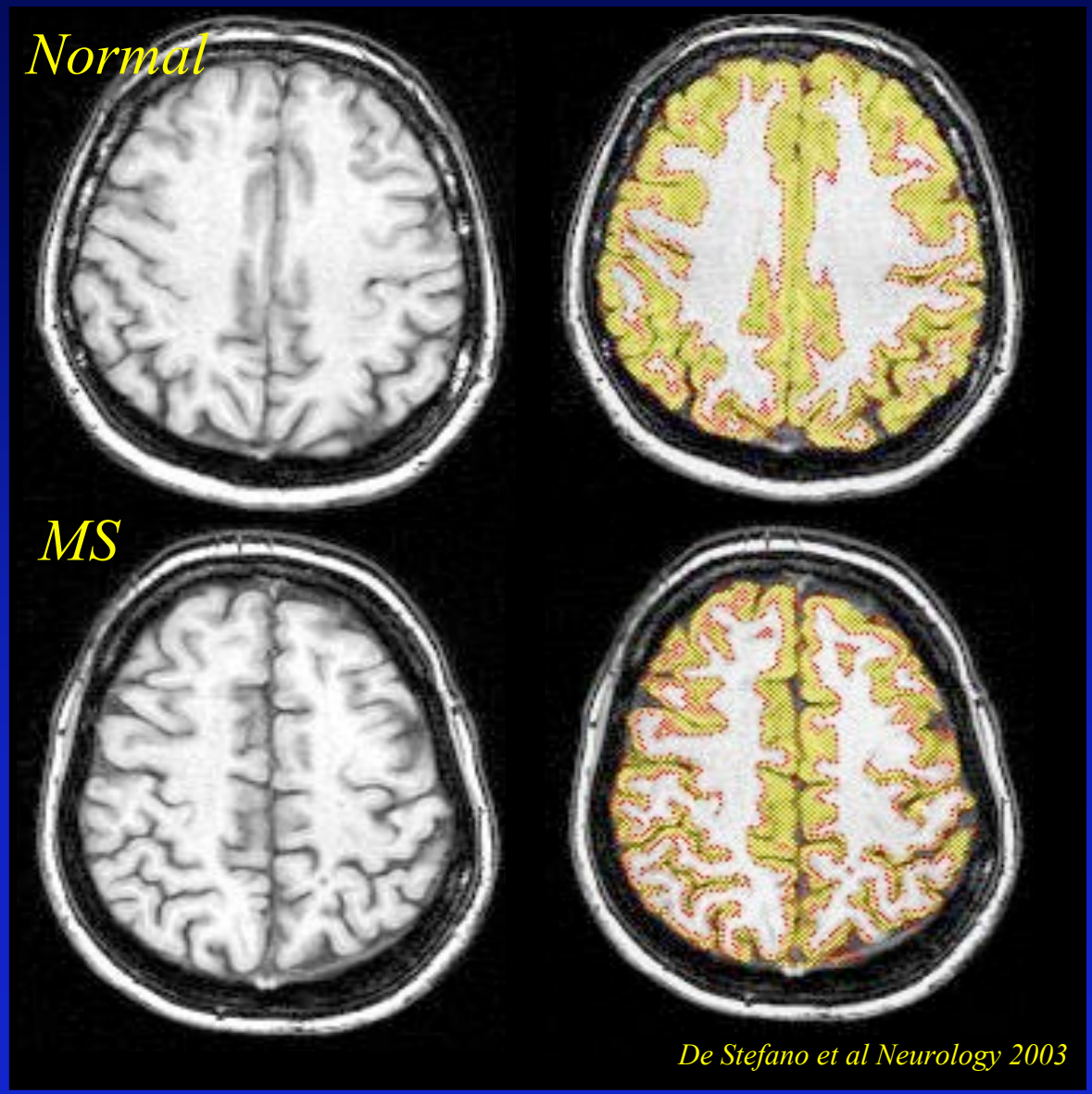


- *Decreases in WM*
- *Increases in Lateral Ventricles*

- *Decreases in GM*

Cortical Volume in Early RR MS

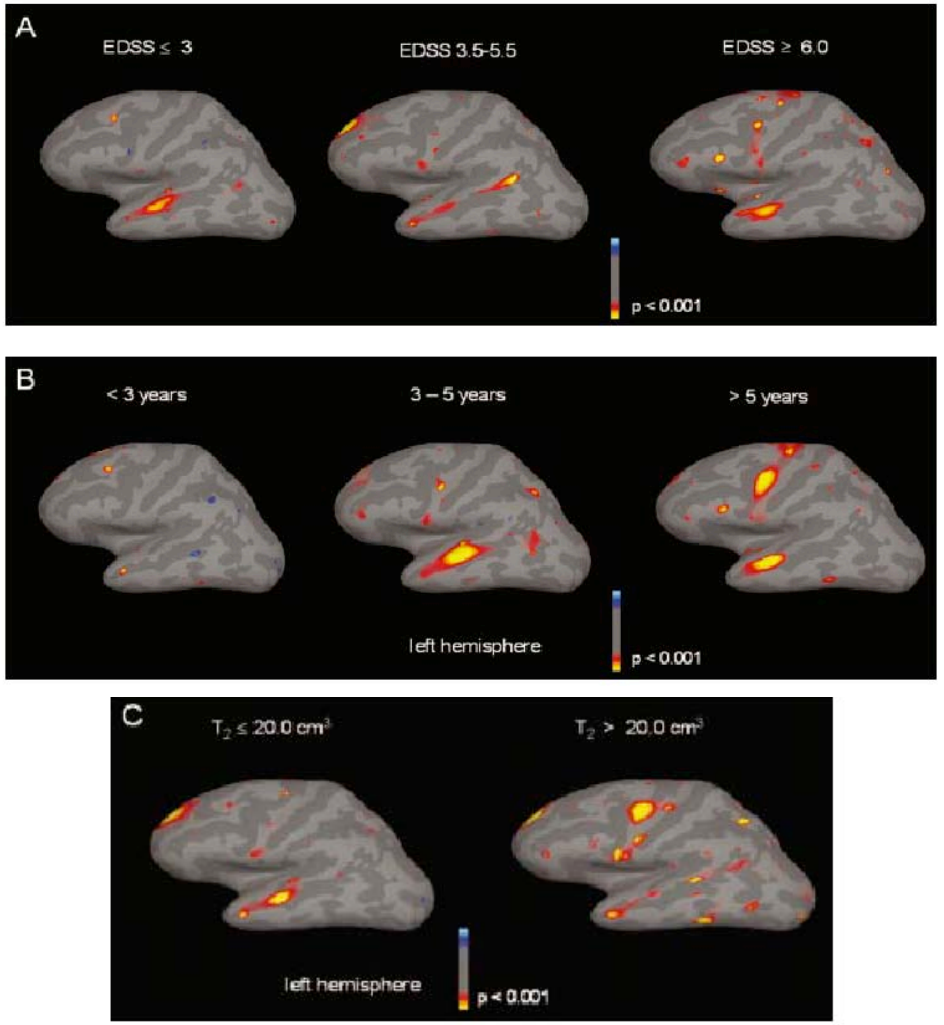


Cortical Thinning in MS Brains

EDSS

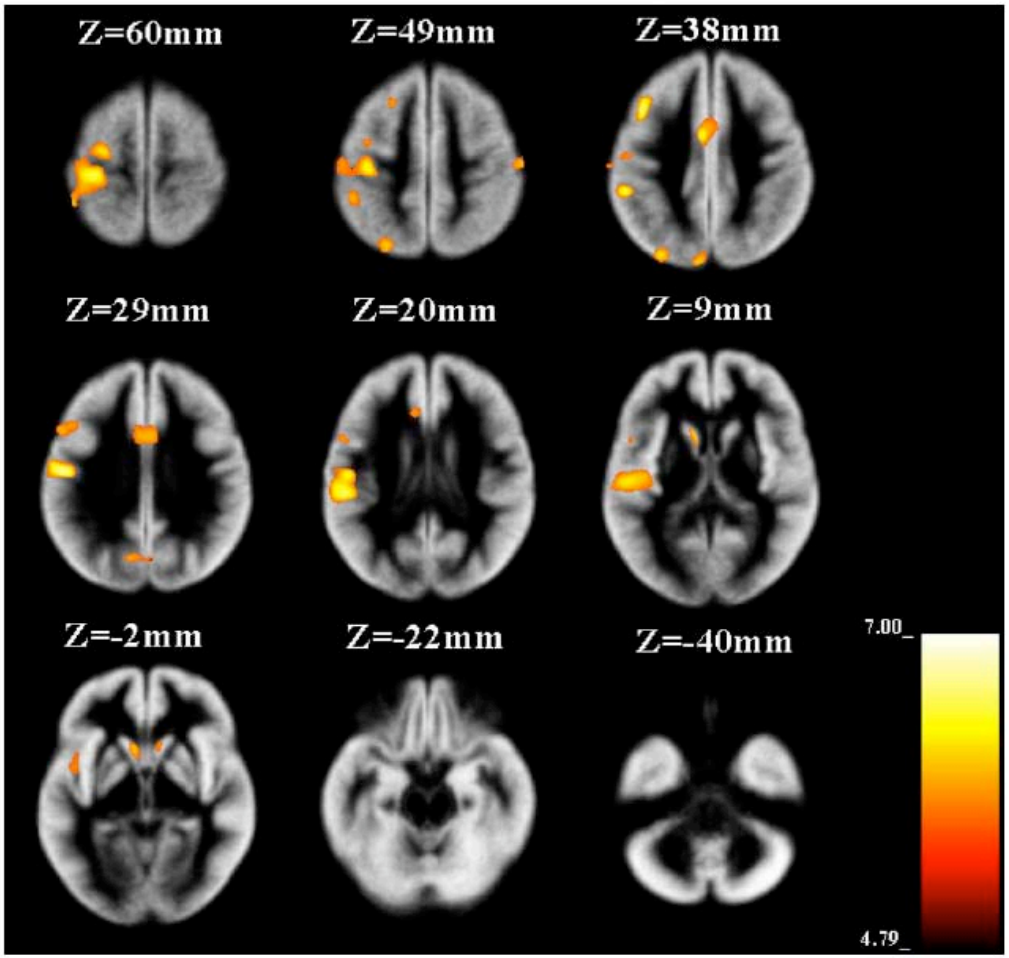
Duration

T2-W Lesions

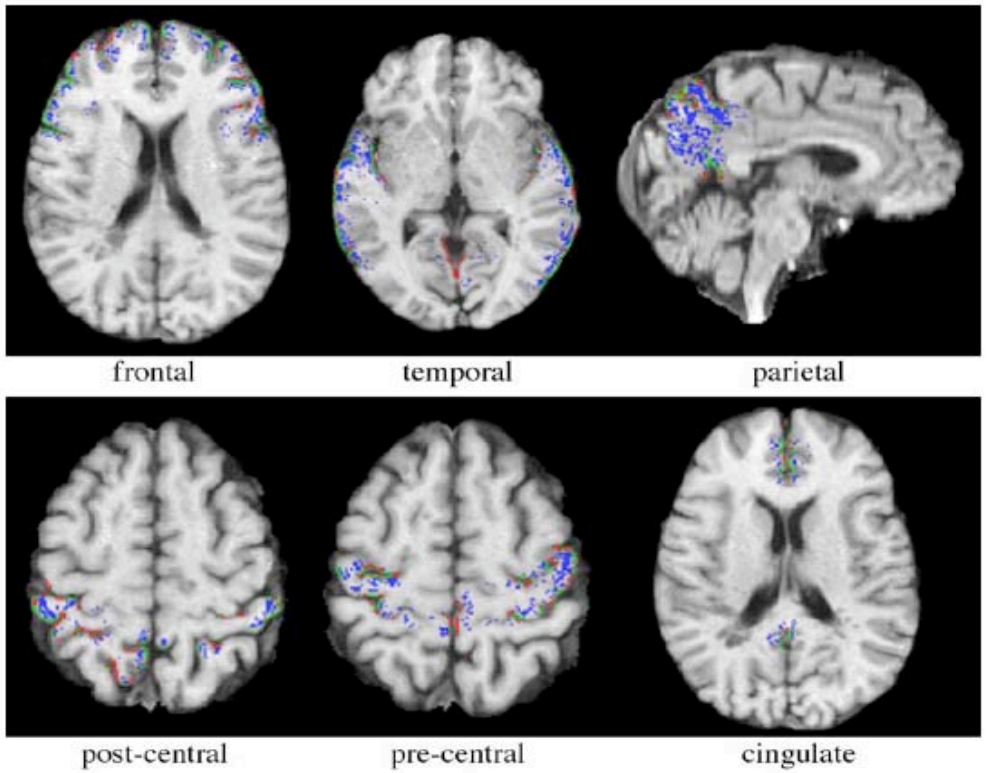


Sailer M et al BRAIN 2003

Cortical Atrophy in MS Brains



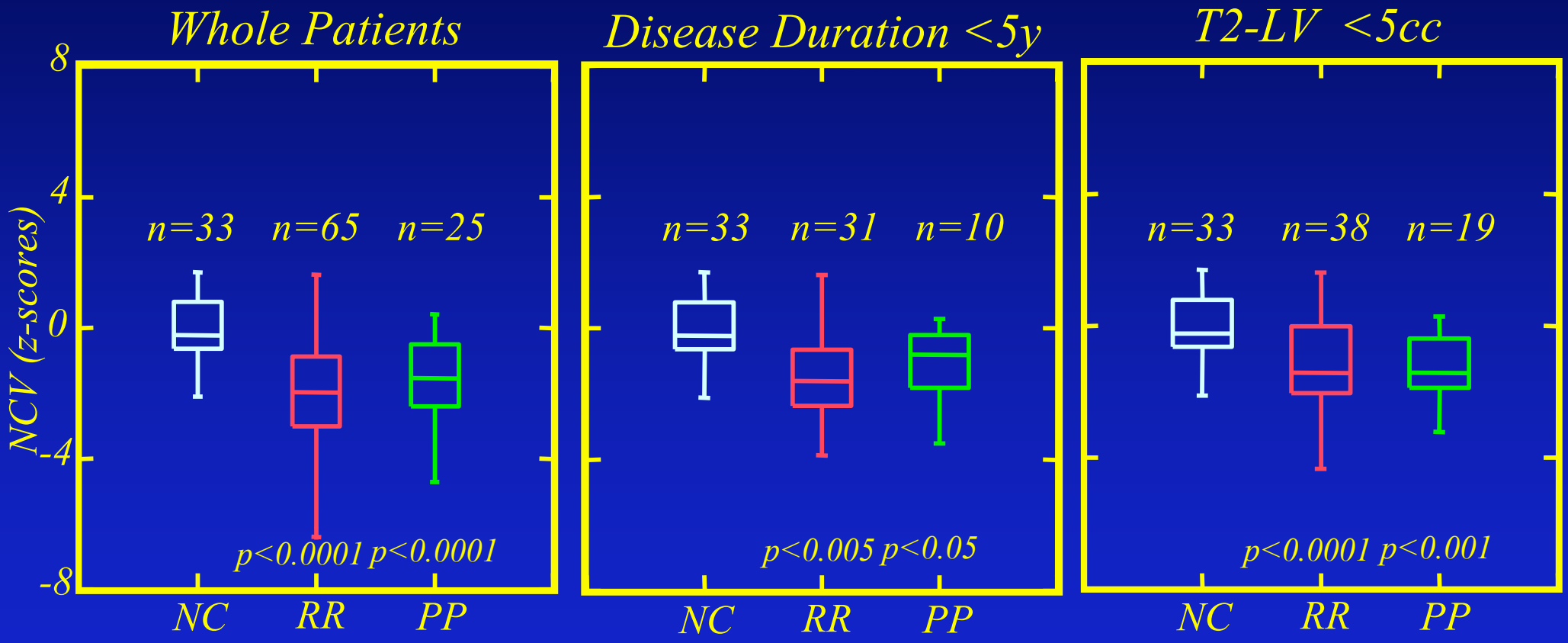
Prinster et al Neuroimage 2005



Chen J et al Neuroimage 2005

Cortical Atrophy in MS

Normal Controls vs RR vs PP

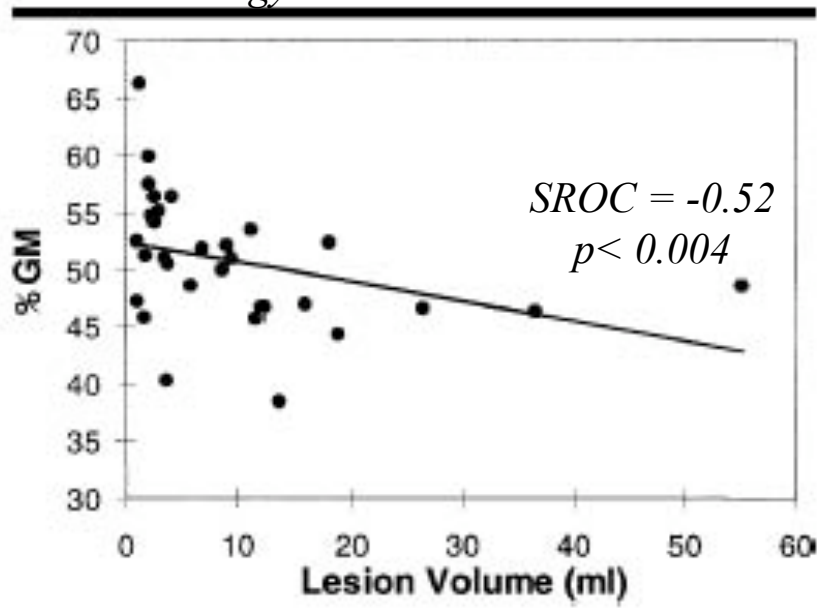


De Stefano et al Neurology 2003

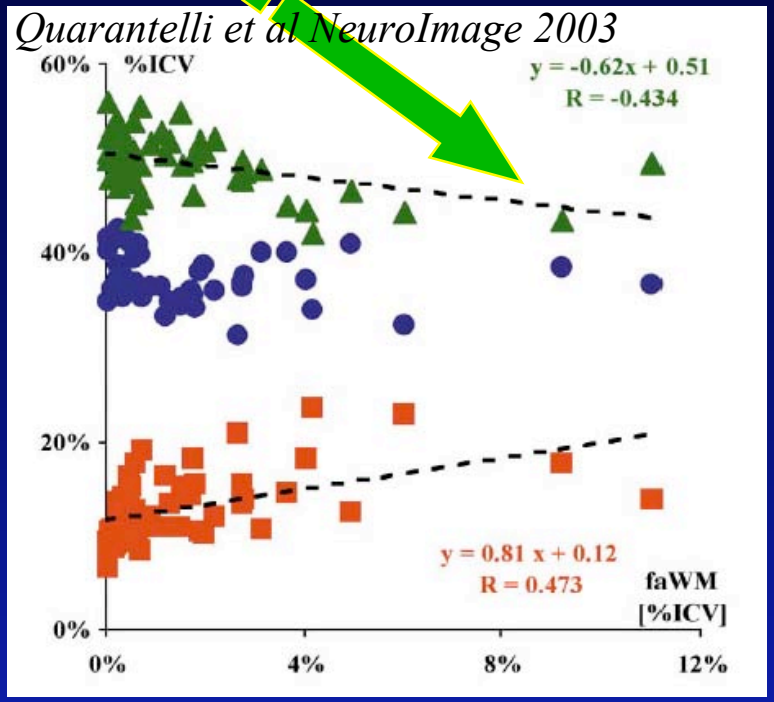
GM Atrophy in RR MS

GM volume vs T2-W LV

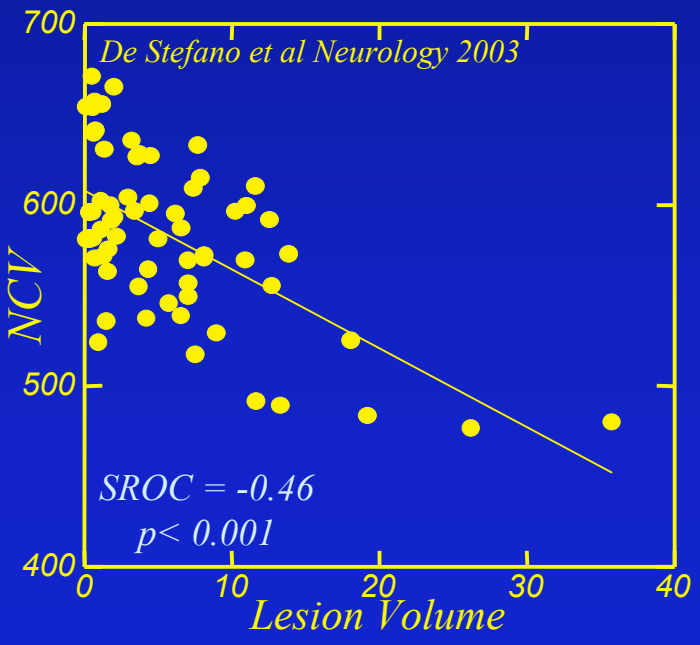
Ge et al Radiology 2001



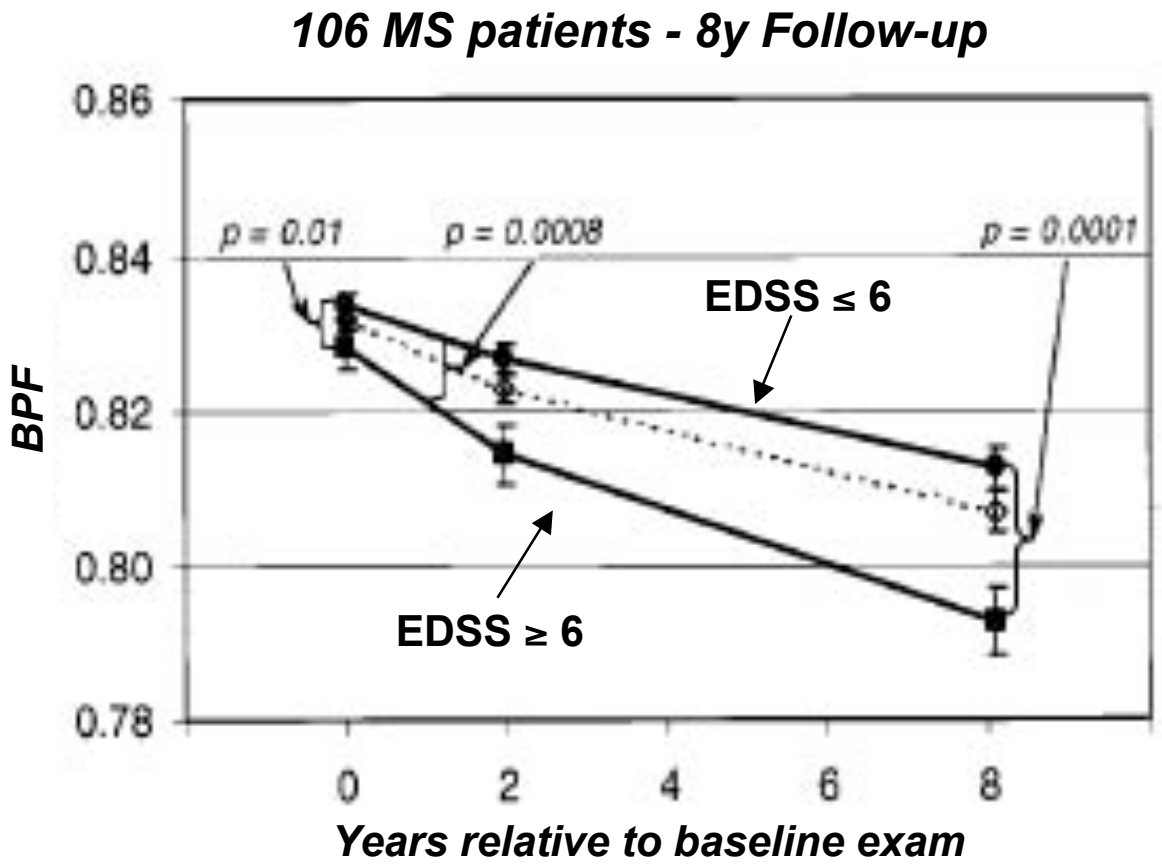
Quarantelli et al NeuroImage 2003



Chard et al Brain 2002
r = 0.53 p < 0.001



Brain Atrophy as marker of disease progression
RR: 8-Year Follow-up



Fisher et al., Neurology 2002

Summary

- *Neuron and Axons are damaged from the earliest disease stages*
- *Lesions are important, but the brain between the lesions is not normal*
- *Cortical damage is common*

Pathogenesis of MS is complex, but includes neurodegeneration from earliest disease stages

Acknowledgements

Alberto Balistreri
Marco Battaglini
Susanna Brogi
Antonio Giorgio
Silvia Marino
Marzia Mortilla
Maria L. Stromillo